96-187

SOFT CONTACT LENS SOLUTIONS: OVERSIGHT OF FDA

HEARING

BEFORE THE

SUBCOMMITTEE ON
OVERSIGHT AND INVESTIGATIONS

OF THE

COMMITTEE ON
INTERSTATE AND FOREIGN COMMERCE
HOUSE OF REPRESENTATIVES

NINETY-SIXTH CONGRESS

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SOFT CONTACT LENS SOLUTIONS: OVERSIGHT OF FDA

TUESDAY, JULY 1, 1980

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE,
Washington, D.C.

The subcommittee met, pursuant to notice, at 10 a.m., in room 2322, Rayburn House Office Building, Hon. Albert Gore, Jr., presiding (Hon. Bob Eckhardt, chairman).

Mr. GORE. The subcommittee will come to order.

I would like to read the opening statement of Chairman Eckhardt, who is unable to be here due to a previous commitment.

The costs of maintaining good health and treating disease in the United States are rising too high and too rapidly. Annual health expenditures in this country average $1,000 for every man, woman, and child—a total of $200 billion each year.

This hearing is another in a series of efforts by the Oversight and Investigations Subcommittee to uncover and combat practices that contribute to skyrocketing health care costs.

Our subcommittee has worked extensively to eliminate wasted health care dollars. Too often, poorly implemented government health programs have resulted in unnecessary and substantial expenditures for health care services. One recent subcommittee hearing revealed that more than $300 million were spent by the Government over the past 5 years for ineffective drugs. Also, the subcommittee identified achievable management improvements in the medicaid program that could save $1 billion per year.

Today we continue this series of hearings with an examination of the salt tablet controversy.

Our investigation indicates that the Food and Drug Administration, whose duties include the regulation of the contact lens industry, is responsible for needlessly imposing substantially higher costs upon users of soft contact lenses. The wearers of soft contact lenses in the United States have unnecessarily spent hundreds of millions of dollars during the past 18 months on new, higher priced contact lens disinfecting solutions. These relatively expensive solutions were substituted in the marketplace for a cheaper agent following an FDA directive to the contact lens industry.

Soft contact lenses were introduced in this country in 1971. At that time, the FDA approved an inexpensive system of cleaning and disinfecting the lenses, using ordinary salt tablets and commercially available distilled water. In 1978, the FDA forced this system off the market, claiming that it had evidence of serious health problems. The FDA action left consumers no alternative but

to purchase a far more expensive, premixed preserved saline solution. And ironically, this preserved solution does cause health problems—for 20 percent of those who use it.

This action by the FDA has dramatically increased the cost of wearing soft contact lenses. The salt tablet system used to cost the consumer about $10 per year. The premixed solution costs from 4 to 10 times as much. When this added cost is passed on to the estimated 4 million users of soft contact lens wearers in the United States, it results in a nationwide increase of $200 million per year in the cost of maintaining the lenses.

During the course of the subcommittee's investigation, questions were repeatedly raised about the process by which the FDA withdrew salt tablets from the market in favor of premixed solutions. Today the subcommittee seeks answers to those questions.

Before hearing from our first witness, I should mention that as our investigation proceeded, we learned that the Inspector General's office in the Department of Health and Human Services had a pending investigation examining some of the same issues. We thereafter coordinated our efforts.

I want to take this opportunity to express appreciation to the Inspector General's office for its splendid cooperation and especially to Mr. Gene Ervin, the assistant special agent in charge of the Inspector General's Washington field office, who has worked most closely with our staff.

In closing, I hope that our hearing today will result in improved procedures within FDA to protect health care consumers without fueling the increase in health costs.

I would now like to recognize our ranking minority member, Mr. Lent.

Mr. LENT. Thank you, Mr. Chairman.

As you know, I strongly believe that, in general, Federal Government regulation of American business is very often unnecessarily overly costly and ineffective. Such regulation should be abrogated whenever possible in order to allow our free enterprise system to operate effectively.

However, when it comes to the health and safety of American consumers, I believe equally strongly that the Federal Government should take the lead.

In the case of new medical devices and new drugs, the FDA is charged with insuring safety and effectiveness.

Because of the obvious extreme importance of their duties, FDA officials are properly held to the highest standards of conduct, especially during the decisionmaking process.

Our inquiry today focuses on FDA regulation of the soft contact lenses industry. Since this is a relatively new industry, many manufacturers and others involved in seeking FDA approval of their lenses, solutions, and devices were understandably unaware of the best way to successfully do business with the Federal Government.

I am therefore particularly interested in the type of regulatory environment created by the FDA officials directly responsible for the regulation of soft contacts. Or, put another way, what sort of face did the FDA show the fledgling soft contact lens industry?

Ultimately, I hope that the subcommittee will be able to determine what is necessary to insure that Federal decisionmaking in

the vital aren of health is completely objective and that Federal officials comport themselves such that their actions, in the words of the HEW standards of conduct, are free from "suspicion of partiality, favoritism, or any hint of conflicting interest."

Mr. GORE. Thank you, Mr. Lent.

Mr. Mottl?

Mr. MOTTL. I have no statement.

Mr. GORE. I would like to call our first witness, Dr. Kenneth Gardner, a medical consultant to this subcommittee.

Dr. Gardner, it is our practice, as you know, to swear all witnesses.

Do you swear to tell the truth, the whole truth, and nothing but the truth, so help you God?

Dr. GARDNER. I do.

Mr. GORE. Please identify yourself for the reporter and then proceed with the presentation of your statement.

TESTIMONY OF KENNETH GARDNER, M.D., MEDICAL CONSULTANT, SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS, COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE

Dr. GARDNER. Mr. Chairman, I am Kenneth Gardner, M.D. I am professor of medicine at the University of New Mexico School of Medicine and a specialist in internal medicine. Since October of last year I have served as a medical consultant to the Subcommittee on Oversight and Investigations. Since April of this year I have participated with subcommittee staff in an investigation of the process by which salt tablets were withdrawn from the soft contact lens marketplace.

My role this morning is to review scientific data as it has evolved around key events in the withdrawal of salt tablets from the market.

Soft contact lenses are made from a plastic that absorbs water. They were approved for sale in this country by the FDA under a new drug application in 1971. Soft contact lenses require careful daily maintenance to minimize risks of infection in the eye and damage to the lens. Soft contact lenses are to be distinguished from hard contact lenses, which are made from a plastic that does not absorb water and which, therefore, requires a different and less arduous system of care. Hard contact lenses have been available in this country since the 1940's.

The use of both hard and soft contact lenses is associated with infection, sometimes serious. In 1966, when only hard contact lenses were available to the public, Dr. Joseph Dixon and his associates reported in the Journal of the American Medical Association that:

> Ophthalmologists in a national survey reported case histories of 14 eyes lost or blinded in patients wearing contact lenses. All of the eye losses were due to infections, four of which were by fungi. There were 157 other eyes permanently damaged and 7,607 with reversible changes.

In 1978, Drs. Krachmer and Purcell wrote in the Archives of Ophthalmology that:

> Soft contact lenses provide a safe alternative to spectacles for more than 1 million patients. However, the hazard of bacterial corneal ulcers exists. This report describes five cosmetic soft contact lens wearers who developed bacterial corneal ulcers.

READEX FICHE

The risk of ocular infection is at the heart of the salt tablet controversy. The substance of that controversy is described in the June 1980 Consumer Reports. I quote selectively:

> Disinfection is one of the daily nuisances and expenses of wearing soft lenses. With heat disinfection, much of that cost is for the saline solution used in rinsing, disinfecting, and soaking the lenses. Until a few years ago, a million or more soft-lens wearers were mixing one Bausch & Lomb salt tablet with one ounce of distilled water to prepare a batch of saline solution to use each day.
>
> In a July 1977 letter to practitioners, Bausch & Lomb touted salt tablets as "safe, effective, economical, and convenient." But, in November 1978, the company decided to stop marketing salt tablets.
>
> The removal of salt tablets from the market outraged many consumers. They wrote angry letters to Bausch & Lomb—charging that the company stopped marketing the tablets because its preserved saline was more profitable. But it wasn't as simple as that. Bausch & Lomb's switch was triggered, in part at least, by the Government's concern over the use of salt tablets.
>
> FDA officials contended that soft-lens wearers were misusing the tablets in several ways: They used the wrong kind of water; the saline they made up was often too salty or not salty enough for the eyes; and most important, their distilled water was often contaminated with bacteria, which could infect the eye.

CU consultants also believe that salt tablets can be used safely—provided they take certain specified precautions. What's more, they point out the tablets are nonirritating and are the least expensive source of saline.

Mr. Chairman, the information made available to subcommittee staff indicates that the bulk of evidence against salt tablets emerged after, not before, a decision was made within FDA to remove salt tablets from the contact lens marketplace.

On December 9, 1976, 23 months before salt tablets were taken from the market, their distributor and the manufacturer of the soft contact lenses with which they were used, Bausch & Lomb, wrote FDA and committed to the phaseout of salt tablets. The Bausch & Lomb commitment was extracted that day at a meeting with Mrs. Mary Bruch, a microbiologist, and Dr. Arnauld Scafidi, an ophthalmologist, the two principal FDA scientists responsible for regulation in the soft contact lens area.

Only 4 months earlier, in July 1976, Dr. Scafidi had reviewed Bausch and Lomb's most recent annual report on their soft lens NDA. This report covered the period of March 1975 through February 1976. Dr. Scafidi concluded with the following recommendation: "Considering the number of lenses dispensed in this country—1,915,294—I feel the incidence of adverse reactions is low but must be carefully monitored."

In September 1977, 9 months after FDA had extracted the commitment from Bausch & Lomb to withdraw salt tablets, FDA awarded $75,000 to the University of Arkansas for a survey of the ophthalmological and optometrical professions. The survey had as its objective the identification of problems associated with the use of soft and hard contact lenses. Dr. Scafidi served as the FDA Project Officer on that study.

Before the results of that survey were obtained, FDA requested in May 1978 that Bausch & Lomb provide a schedule for the immediate withdrawal of salt tablets from the marketplace.

The letter of request, while sent from FDA's Bureau of Medical Devices, originated in FDA's Bureau of Drugs, and was drafted by Mrs. Bruch. The letter cites the Krachmer-Purcell study as evidence of the risks of eye infection to users of salt tablets. Krachmer

and Purcell, however, did not specifically implicate salt tablets, but instead summarized as follows: "Possible sources of contamination are discussed, but in no case was it determined."

The survey contract terminated in August 1978. Its results were filed in three places: In the file of FDA Contract No. 223-76-3018 in the form of a computer printout; in the archives of FDA's Bureau of Medical Devices in the form of copies of the submitted responses; and in the registry of drug-induced ocular side effects, initially maintained at the University of Arkansas and later at the University of Oregon.

In neither the contract file nor in the registry printout dated July 1978–June 1979 are salt tablets listed as an agent causing adverse reactions. However, the raw data at the Bureau of Devices contain, by my count, approximately 67 instances of serious eye infection and corneal ulcers, among 1,093 responses from physicians caring for wearers of all types of contact lenses.

Of the ulcers, 19 were reported in association with the pseudomonas organism; 4 of the 19 occurred among wearers of hard contact lenses. Hence, the maximum possible soft lens pseudomonas adverse reaction is 15. The number of ulcers among salt tablet users cannot be determined from the data on file. Two ulcers, however, are described in users of preserved saline.

During the year 1979–80, the registry of drug-induced ocular side effects continued to enter responses to the survey. The printout for that year for the first time lists salt tablets as an agent associated with adverse reactions in the eye. Two hundred and one patients are listed as having suffered adverse reactions while using salt tablets. Of these 201 patients, 196 were reported at one time as case report No. 1810, which was received by the registry in August of 1979.

In May of this year the registry sent to the subcommittee a copy of case report No. 1810. The report, which was forwarded to the registry by cassette tape, was transcribed as follows:

> Sodium chloride tablets 1810. Quick update: "I have here now 196 cases of corneal infections secondary to salt tablets. These have been documented by the doctor. All of these incidentally, the case and the lens as well as the patient's eye were cultured. Believe this or not, 10 cases of pseudomonas, 6 fungal infections, about 12 staphylococcal infections and just about all the rest of them are [text missing] except for two. There are two streptococcus ulcers and these are an anaerobic bug. Of these infections 22 of them have now gone to corneal transplant. All these patients were using a salt tablet. None were using preserved saline.

In May 1980 the registry advised staff that the originator of case report No. 1810 was Dr. Arnauld Scafidi.

The numbers cited in this case report do not agree with data filed at FDA, including the Drug Experience Network reports, B. & L. annual reports, the file of contract No. 223-76-3018, nor copies of the survey responses. Nor do they appear in a recently prepared summary of the survey experience originating in the Bureau of Medical Devices.

They do, however, coincide with a listing of adverse reactions associated with the use of salt tablets. The listing was submitted as an attachment to a memorandum dated April 18, 1980, and signed by Dr. Scafidi, notifying the Bureau of Medical Devices of a notebook in which is listed data that he personally collected from clinicians. [See p. 41.]

In summary, Mr. Chairman, subcommittee staff was unable to document among the records of FDA evidence that salt tablets are relatively unsafe. In fact, during an interview with staff on April 21, 1980, Dr. Scafidi stated that the only data he has on clinical cases is what is regarded as soft.

Mr. Chairman, during my presentation I have referred to a number of documents. I now would like to submit those documents for inclusion in the record, together with a summation of the events that I have described, and a tabulation of the data available concerning the hazards of soft contact lens wear and salt tablet usage.

Thank you.

Mr. GORE. Thank you, Dr. Gardner.

Without objection, the documents to which you referred will be included in the record at this point. They are labeled "Dr. Kenneth Gardner exhibits." They are marked "A" through "N."

I would also ask unanimous consent to put into the record at this point a salt tablet chronology marked 1 through 20.

[Testimony resumes on p. 126.]

[The material referred to follows:]

DR. KENNETH GARDNER
EXHIBITS

A. FDA Approval of NDA 16-895 (Bausch and Lomb soft contact lens).

B. Dixon Article: JAMA 1966.

C. Krachmer-Purcell Article: Arch. Ophthal. 1978.

D. Consumer Reports: The Controversy over Salt Tablets, June 1980, p. 386.

E. Letter, December 9, 1976.

F. MO's Review of ND 16-895, July 19, 1976.

G. Modification I Contract #223-76-3018 (pages 1 & 2 of 7 pages).

H. Letter, May 1, 1978 : Food and Drug Administration to Bausch and Lomb.

I. Registry Print-Out, July 1978 - June 1979, (page 1 of numerous pages).

J. Registry Print-Out July 1979 - June 1980, (three of three pages and letter from Director of Registry).

K. Registry Transcript of Case Report #1810.

L. Food and Drug Administration/Bureau of Medical Devices Draft of Contact Lens Survey received May 28, 1980.

M. Memorandum: Dr. Scafidi, April 18, 1980.

N. Memorandum of Meeting Submitted by Edward Melton, Food and Drug Administration.

Gardner (A)

NDA 15-093

AF 36-809

MAR 18 1971

Bausch and Lomb
Soflens Division
Attention: Mr. William F. Coombs
635 St. Paul Street
Rochester, New York 14602

Gentlemen:

This acknowledges the receipt on March 16, 1971 of your communication dated March 16, 1971 enclosing printed labeling pursuant to your new drug application for "Soflens™ Contact Lens (polymacon)".

We also acknowledge your previous communication of March 9, 1971.

The application was filed on March 16, 1971.

We have completed the review of this application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is APPROVED.

The enclosures summarize the conditions relating to the approval of this application.

Please submit two market packages of the drug when available.

Sincerely yours,

Henry E. Simmons, M.D., M.P.H.
Director
Bureau of Drugs

Enclosures:
Records and Reports Requirement (Reg. 130.13)
Conditions of Approval of NDA

cc: HFD-80
NDA 15-093 orig., dup.
15-093 (HFD-12 HFD-32 HFD-242 HFD-1
D/D-Lachance-3/16/71
D/D Arth, Kleinerts, Richards-3/16/71
Typed final-cm-3/16/71

Microbiological challenge of the Asoptor Unit was conducted using the following organisms: Candida albicans, Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtilis and Herpes simplex.

No growth was evidenced in the culture tubes. The results indicate that the efficiency of the Soflens™ Asoptor units and submersion in boiling water are comparable.

Control Numbers: 5(a) — Satisfactory. A detailed explanation of the lot numbers is provided and illustrated by an example.

Stability: 6(p) — Satisfactory for the market package. Package stability tests include shelf life determination test, body temperature life test, accelerated life test, low temperature test, fitting set Asoptor test and freezing test.

Samples and Results: 505(b)(5) — Satisfactory. Samples submitted according to regulations, properly coded and accompanied by a protocol.

Labeling: — Satisfactory. The following draft labeling has been submitted:

1. Shipping vial label.
2. Label placed on outside of styrofoam shipper.
3. Plastic sleeve.
4. Label on bottle containing sodium chloride tablets.
5. Label on one ounce plastic container for normal saline solution.
6. Package insert.
7. Instructions for wearers of Soflens™ Contact lenses.

GARDNER: (B)

Complications Associated With the Wearing of Contact Lenses

Joseph M. Dixon, MD, Charles A. Young, Jr., MD, Joseph A. Baldone, MD, G. Peter Halberg, MD, Whitney Sampson, MD, and William Stone, Jr., MD

Ophthalmologists in a national survey reported case histories of 14 eyes lost or blinded in patients wearing contact lenses. All of the eye losses were due to infections, four of which were by fungi. There were 157 other eyes permanently damaged and 7,607 with reversible changes. These physiologic and pathologic eye changes indicated the medical problems of diagnosis, treatment, and routine follow-up of these patients.

The popularity of contact lenses has exceeded the public knowledge of potential hazards associated with their use. The Committee on Contact Lenses of the American Association of Ophthalmology (formerly the National Medical Foundation for Eye Care) conducted a survey of American ophthalmologists to determine the extent of these medical problems. This is a report of that survey.

The ocular complications of the wearing of contact lenses reported in this study may be divided into three groups: (1) eyes removed or blinded (corrected vision not more than 20/200); (2) eyes and/or vision permanently damaged (corrected vision more than 20/200); (3) reversible ocular changes.

Procedure

Questionnaires were mailed to ophthalmologists covering contact-lens experience with new patients or patients recalled during the 12-month period prior to the survey, April 1960. There were 8,181 questionnaires mailed, of which 1,904 were returned. Of the 49,954 patients wearing contact lenses seen by the reporting ophthalmologists during the 12-month period, 36,777 patients had contact lenses prescribed by the reporting ophthalmologists, and 13,177 had contact lenses not prescribed by the reporting ophthalmologists.

Results of Survey

Group 1

This group includes cases in which eyes were removed or blinded because of contact-lens wearing or associated factors. Available information does not include all data on types of lenses, wearing habits, and complete laboratory reports. Each case was reported by an ophthalmologist as a complication of wearing contact lenses. The cases were reported from widely scattered states in the nation.

CASE 1.—A 56-year-old Arizona woman with bilateral aphakia and small iris prolapse with filtering bleb in each eye had been fitted with contact lenses by her ophthalmologist about six months after surgery in 1960 and had found the vision far superior to conventional glasses.[1]

In early July 1961, the lenses were returned for adjustment. On subsequent examination, these lenses showed no defects or roughness of the edges or surface. During the time the patient was without lenses, there was purulent conjunctivitis which had cleared by the time the lenses were returned to her. The lenses were worn only two or three hours daily for five days after their return.

On the sixth day, the left eye was uncomfortable and red. That afternoon the patient's ophthalmologist found the bulbar conjunctiva diffusely red, a minimal purulent exudate, and a 1+ flare and cells in the anterior chamber, and no staining of the cornea with fluorescein. Systemic and topical administration of chloramphenicol was started immediately, but the next morning there was purulent endophthalmitis. The right eye was normal.

The patient was hospitalized, and cultures were taken from the conjunctival sac for bacteria and fungi. The only organism recovered was nonhemolytic *Staphylococcus albus*, coagulase negative. Penicillin, chloramphenicol, and adrenal corticosteroids were given systemically. The eye gradually improved, and the patient was discharged from the hospital Aug 5. At the time of the report, the vitreous body was cloudy and the vision reduced to light perception.

Wild[1] expressed the opinion that the contact lens partially eroded a conjunctival bleb, allowing organisms from the purulent conjunctivitis present the previous week to enter the eye. The patient also had a habit of using saliva as a wetting agent.

CASE 2.—A corneal abrasion developed in a 46-year-old woman with aphakia, while wearing contact lenses. The abrasion resulted in an ulcer which required the patient's hospitalization to save the eye, but scarring of the cornea reduced the vision to counting fingers. The abrasion had appeared after the patient put both lenses on the same eye by error.

CASE 3.—A woman was fitted with bilateral contact lenses one year after cataract surgery. The left eye had a filtering bleb at the 12-o'clock position which had resulted from a wound dehiscence. There was also bilateral glaucoma, but the patient decided to wear the lenses in spite of being warned about the dangers.

During the year after receiving the contact lenses, the patient was examined at regular intervals for glaucoma, which was controlled. After wearing the lenses for one year, an acute fulminating endophthalmitis developed in the left eye, which had the filtering bleb. The infection subsided after the patient's hospitalization and intensive

From the Committee on Contact Lenses of the American Association of Ophthalmology, Washington, DC.

Reprint requests to American Association of Ophthalmology, 1100 17th St, Washington, DC 20036.

AMA Arch Ophth—Vol 195, March 14, 1962

antibiotic treatment, but the vision was reduced to perception of hand motion. Four months later the eye was enucleated because of recurrent redness and irritation. Pathological examination showed inflammation of the posterior of the eye and retinal detachment.

It is interesting that the optical company where the patient obtained her lenses had also furnished a contaminated solution despite the fact that this solution had been removed from the market.

CASE 4.—A woman, aged 32, was fitted with contact lenses prescribed by her ophthalmologist. The patient had been wearing contact lenses without difficulty until, one evening after returning from a party, she fell asleep while wearing the lenses. The following morning she awoke with pain, redness, and blurred vision in the right eye.

She went to her ophthalmologist, who treated her with drops. The eye improved for three days, then became worse. Six days after the onset of the complication, she was admitted to the hospital in a university medical center. There was a deep, dense ring abscess of the right cornea. *Pseudomonas fluorescens* was identified as the pathogenic organism. The cornea perforated, endophthalmitis developed, and the eye was eviscerated.

CASE 5.—A fungus infection in a corneal abrasion developed in a male patient in a veterans' hospital while wearing contact lenses obtained elsewhere. The cornea perforated and the eye was lost.

CASE 6.—A woman was referred to an ophthalmologist by her family physician because of pain in the right eye, with intense inflammation of the eye ball secondary to a central corneal ulcer and iritis. A central corneal erosion due to a contact lens was present in the left eye. She reported that she had recently been fitted with a new pair of contact lenses.

The abrasion of the left eye healed, but the infection in the right eye grew worse, and a consultant advised a conjunctival flap operation to cover the ulcer. This was done. Cultures were positive for *Candida albicans*. Two months later the ulcer had healed, but iritis persisted, and the flap was removed on advice of the consultant. The eye was uncomfortable and the vision less than 20/200 due to scarring and irregular astigmatism.

CASE 7.—A corneal abscess in the right eye developed in a man fitted with contact lenses, after wearing a contact lens for three days. The eye had previously had a scleral-buckling operation for detached retina. *P aeruginosa* was recovered from the ulcer. The infection was later controlled, but severe corneal damage reduced the vision to light projection only.

CASE 8.—A corneal erosion developed in a young woman fitted with contact lenses; she had secondary infection when first seen by an ophthalmologist several days after onset. The eye was enucleated because of endophthalmitis.

CASE 9.—A 39-year-old woman whose case has been reported previously[2] was fitted with scleral lenses in 1947. In 1960, the scleral lenses were changed to corneal lenses. In July 1961, several small, deep, whitish-gray corneal lesions appeared in the right eye near the center. The eye responded well to treatment with a corticosteroid and atropine and three weeks later had healed with a small, deep corneal scar.

On Sept 21, after she had started wearing contact lenses again on a limited basis, the patient was struck in the eye by her child's hand. On Oct 24, the patient was admitted to the hospital with a recurrence of the previous ulceration of the same cornea, which perforated. After more than five months of the patient's pain and misery, the eye was enucleated in December. Cultures and microscopic sections were positive for *C albicans* in the cornea and anterior chamber.

CASE 10.—A 50-year-old woman wore a therapeutic contact lens for inactive Stevens-Johnson syndrome. A corneal abscess due to *Monilia (Candida)* developed. The infection was controlled, but the cornea became vascularized with visual acuity reduced to hand motion.

CASE 11.—A 49-year-old man who had keratoconus had been fitted with scleral lenses. The lenses corrected the vision to 20/30. Ulceration of the left cornea developed, which required suturing of his eyelids. The ulcer healed with a large corneal scar. A corneal transplant was necessary, and it improved the corrected vision to 20/50.

CASE 12.—A 40-year-old housewife who had been wearing contact lenses was admitted to a hospital as an emergency because of purulent keratitis with hypopyon of the right eye. She was first seen by an ophthalmologist four days after onset of pain. The cornea was entirely gray and completely denuded of epithelium. It healed with vision reduced to less than 20/200. There was no growth on culture.

CASE 13.—An unmarried woman, aged 33, had a perforating wound of the left cornea and traumatic cataract which was treated by linear extraction. This procedure resulted in a small corneal scar, but the vision corrected to 20/30, with a correction for aphakia.

One year later, the patient returned to her ophthalmologist with a purulent corneal ulcer and endophthalmitis. The aphakic eye had been fitted with a contact lens without the knowledge of her ophthalmologist. The eye had been scratched and the infection had developed. The patient was hospitalized, but did not respond to medical treatment. The eye was enucleated. On pathological examination, keratitis with perforating wound of the cornea and endophthalmitis was diagnosed at the Armed Forces Institute of Pathology.

CASE 14.—A woman with bilateral aphakia of three years' duration was examined by a consultant because of pain in her right eye four months after wearing a contact lens prescribed by a physician. There was chronic keratitis of the right cornea with epithelial edema. The left eye had central guttate keratitis but was asymptomatic. Four months later, the patient was hospitalized for a corneal ulcer in the right eye. This ulcer healed but vision was not recovered. A corneal transplant was necessary. Alcohol was given retrobulbarly for relief of pain, and the visual acuity in that eye was light perception only.

Since the time this survey was made, three additional cases of eyes blinded while wearing contact lenses have been reported to this committee or to the association.

Group 2

This group includes cases of eyes permanently damaged by scars or other defects which may or may not partially impair the vision. Cases of opacities of the cornea and permanent scarring were reported by 137 physicians.

Group 3

This group includes any reported cases of damage from which patients recovered without permanent defects.

1. Epithelial staining	5,194
2. Deep corneal opacity (any reduction in transparency)	276
3. Corneal ulceration	468
4. Edema of the corneal stroma	645
5. Traumatic iritis	107
6. Descemet's membrane wrinkling	101
7. Activation of corneal diseases not usually associated with but probably due to contact lenses	616
Total	7,907

of the patients in groups 2 and 3 were ized, but this tabulation was not included uestionnaires.

Comment

only incident of blindness in both eyes by contact lenses was reported previously au and Perdriel[2] in 1956 and is not included eries.

rvations to be made of these eyes blinded or d by contact lenses are as follows:

ne wearing of contact lenses is an abnormal n which can result in serious medical com-ns.

ese complications may require prompt l diagnosis and treatment.

all cases in which the eye was removed or there was infection. In ten cases this was al or due to unidentified organisms, in four was due to fungi. It should be pointed out e wearing of contact lenses on the normal h proper technique, does not alter the nor-cterial flora.[4]

f the 14 cases reported of eyes blinded, one used contact lenses for therapeutic reasons, irregular refraction due to keratoconus, one nocular aphakia. Eleven of these 14 patients ontact lenses for possible optical and cosmetic ages over spectacles. Six patients required al of the eye. Two required corneal-graft op-s; only one of these patients recovered vi-ut in that instance the final vision of that eye duced to 20/50.

This survey, as well as the clinical experiences authors, shows that complications associated with the use of contact lenses are more frequent in eyes with aphakia or filtering wounds, in patients in the older age groups, and in eyes with previous injury or disease and that complications are associated with prolonged wearing time or with sleeping with the lenses on the cornea. These complications are made more severe by wearing the lenses after the complications appear.

6. The responsibilities of the ophthalmologist include the following: (a) examination and evaluation of the eye and the patient; (b) making certain that the patient is supplied with properly constructed lenses that correctly fit the individual patient with a minimum of corneal changes; (c) instruction of the patient in proper lens handling, insertion, and removal techniques, cleaning and storage of the lenses; (d) prescription of wearing schedules; (e) follow-up care at regular intervals; (f) diagnosis and treatment of complications.

This survey and previously published clinical and laboratory studies suggest that the majority of patients wearing contact lenses have some degree of alteration of the ocular tissues, changes in the corneal metabolism, or other medical problems associated with their use.[5]

Louis A. Bredfeldt, MD, Alexander M. Calonde, MD, Frank E. Duffy, MD, Edward A. Hasbrouck, MD, N. D. Robinson, MD, William Stone, Jr., MD, John J. Wild, MD, and other ophthalmologists supplied case histories of the 14 patients in group 1 and authorized their publication.

Other physicians who served on the Committee on Contact Lenses during this study are Morris Feldstein, MD, Louis Girard, MD, Edwin C. Tait, MD, J. Wesley McKinney, MD, Barnet R. Sakler, MD, Edwin S. Stone, MD, Frederick E. Hasty, MD, and Chester J. Black, MD.

Generic and Trade Names of Drug

Chloramphenicol—Chloromycetin.

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BOOK REVIEW.—*Transactions of the American Medical Association.* The present volume, like many of its predecessors, while presenting an interesting account of the proceedings at its annual meeting, together with a number of very good and instructive papers, is remarkable for the absence of any really new and original contributions to the sum of scientific knowledge. Of course, no one can peruse the volume without experiencing much pleasure and no little profit; but at the same time we must admit that greater things might reasonably be expected of the national Association of a great people—greater in nothing than its youthful attainments in the science and art of medicine. We entirely agree with Dr. Sayre, in his Presidential address, that it would be far better for the Association to inaugurate and publish such a weekly as the *British Medical Journal*, than to continue to issue "the present bulky, tardy, little read and unproductive volume of Transactions." This one idea we deem to be the most pregnant with profit in this edition.—Book Notices, *Can J Med Sci* 9:161-162, 1851.

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Bacterial Corneal Ulcers in Cosmetic Soft Contact Lens Wearers

Jay H. Krachmer, MD; John J. Purcell, Jr, MD

• Soft contact lenses provide a safe alternative to spectacles for more than 1 million patients. However, the hazard of bacterial corneal ulcers exists. This report describes five cosmetic soft contact lens wearers who developed bacterial corneal ulcers. In three cases, the resulting visual acuity was 6/120 or less. Possible sources of contamination are discussed, but in no case was it determined.

(Arch Ophthalmol 96:57-61, 1978)

Soft contact lenses are now a well-accepted alternative to hard contact lenses or spectacles for the correction of refractive problems. Approximately 1.3 million patients are currently wearing soft contact lenses, according to C. Titus (oral communication, March 1977). A search of the literature has revealed only one culturally proved case of bacterial corneal ulcers in patients who were soft contact lenses for cosmetic reasons.[1]

In the past year, five patients who were cosmetic soft contact lens were referred to us because of culturally proved bacterial corneal ulcers. The seriousness of these cases ranged from easily treatable with resulting 6/6 visual acuity to cases of severely damaged visual acuity that required keratoplasty. The purpose of this communication is to describe these five cases and, thus, to remind those who prescribe soft contact lenses that, although the chances are overwhelming that their patients will not develop seriously damaging problems, the possibility does exist.

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REPORT OF CASES

Case 1.—An 18-year-old woman had worn soft contact lenses for two years without difficulty. She had sterilized the lenses every night by boiling them in saline solution that she prepared fresh every other day.

On Feb 14, 1976, she started to have a foreign body sensation beneath the left lens and, therefore, she discontinued wearing the lenses. The discomfort progressed to severe pain, so later that day she saw her local physician, who started antibiotic therapy. Her condition did not appear to be improving, so she was referred to the Ophthalmology Department at the University of Iowa, Iowa City.

On admission, Feb 23, 1976, she was in obvious discomfort from ocular pain. Visual acuity was 6/6 OD and light perception with good projection OS. Results of ocular examination OD, besides myopia, were normal.

On the left eye, she had lid edema, conjunctival hyperemia and edema, and a moderate purulent discharge. A 4-mm central, corneal ulcer that extended to midstroma with infiltration at the base and margins was present (Fig 1). The surrounding corneal tissue was edematous. Severe anterior chamber exudation included a fibrinous iritis and a 3-mm hypopyon. She had a very large, tender left preauricular lymph node.

A platinum spatula was used to obtain material from the base and margins of the corneal ulcer for stains and cultures. Gram's stain of this material and from a repeated scraping did not reveal any organisms.

Therapy was started, with the assumption that the ulcer was bacterial. The patient was allergic to penicillin by history. Vancomycin hydrochloride (25 mg) and gentamicin sulfate (20 mg) were given subconjunctivally. Gentamicin sulfate (3 mg/ml) and a mixture of polymyxin B sulfate, neomycin sulfate, and gramicidin (Neosporin) (commercial strength) were given topically once an hour, with the gentamicin dosage on the hour and the Neosporin dosage on the half hour. Twenty percent topical acetylcysteine four times each day and 0.25% scopolamine hydrobromide three times each day were also administered.

The following day she was much more comfortable, she had considerably less discharge, and the preauricular lymph node was smaller and less tender. The subconjunctival injections were repeated.

On Feb 25, 1976, *Pseudomonas* was isolated on culture, and was later identified as *P aeruginosa*. By in vitro antibiotic sensitivity studies, the organism was sensitive to gentamicin, polymyxin B, carbenicillin disodium, trisulfapyrimidines (Triple Sulfa), and colistimethate (Coly-Mycin M Parenteral) sodium and resistant to methicillin sodium, oxacillin sodium, chloramphenicol (Chloromycetin), streptomycin sulfate, a mixture of phenoxymethyl penicillin and trisulfapyrimidines (V-Cillin tri-

68-106 O—80——2

fa), erythromycin ethylsuccinate, ampicillin, neomycin, bacitracin, tetracycline hydrochloride, kanamycin sulfate, and cephalothin (Keflin) sodium. Half of the ulcerated cornea had epithelialized, and we were confident that the infection was well controlled by our antibiotic regimen. Therefore, a regimen of 1% topical prednisolone acetate twice each day was started, and we hoped this regimen would lessen eventual postinflammatory scarring.

Subconjunctival gentamicin was repeated for two more days. Vancomycin was not repeated. Gentamicin and Neosporin drops were continued but with less frequency. She was discharged on March 2, 1976.

The regimen of topical prednisolone, scopolamine, gentamicin, Neosporin, and acetylcysteine was continued with varying frequencies as the cornea healed. A resulting irregular, scarring cornea reduced her best corrected visual acuity to 6/120 on Aug 31, 1976 (Fig 2).

Cultures of the contact lens were negative. The contact lens case and solutions were not cultured.

CASE 2.—A 21-year-old woman had worn soft contact lenses for three years without difficulty. She claimed she sterilized the lenses nightly by boiling them in saline solution that she prepared fresh every three to four days.

Six days prior to admission, she noticed a scratching sensation in the left eye, and she stopped wearing both lenses. The problem increased so that two days later she had substantially decreased visual acuity, pain, and discharge. She waited two more days to see a physician, who started therapy with topical atropine sulfate and Neosporin eye drops and penicillin for systemic effects. The next day there was no improvement, so the patient was referred to the Ophthalmology Department at the University of Iowa.

On admission, July 22, 1976, her uncorrected visual acuity was 6/30 OD and light perception with poor projection OS. Her condition improved to 6/7.5 OD with a pinhole, but did not improve OS. Besides myopia, no ocular abnormalities were found OD.

The left cornea was ulcerated to a third of the normal thickness with infiltrate at the base and margins of a 7-mm ulcer (Fig 3). The nonulcerated rim was edematous. The conjunctiva was inflamed and exhibited injection, edema, and a moderate amount of purulent discharge. The lower third of the anterior chamber contained a fibrinous exudate. The intraocular pressure was 16 mm Hg by Mackay-Marg applanation.

Scrapings of the base and margins of the ulcer were performed. The material was used for Gram's and Giemsa's stains and fungal and bacterial cultures. The left contact lens and the wetting solution were also cultured. The contact lens case was not cultured.

Careful examination of Gram's stain failed to reveal organisms. The corneal ulcer was still assumed to be bacterial and treated accordingly. Gentamicin sulfate (20 mg) and methicillin sodium (100 mg) were given subconjunctivally, and gentamicin sulfate (8 mg/ml) and Neosporin (commercial strength) were applied topically every hour. Before each antibiotic instillation, the mucopurulent exudate was removed. Ten percent phenylephrine (Neo-Synephrine) hydrochloride and 0.25% scopolamine hydrochloride were each applied three times each day. Subconjunctival injections of gentamicin and methicillin were repeated daily for three days.

By the second and third day after admission, the eye was responding to the therapy with less discharge; the eye had a much smaller hypopyon, and there was less inflammatory necrosis of the ulcer. On the third day, the laboratory identified *P aeruginosa* on culture. Antibiotic sensitivity studies were identical to case 1, except for a resistance to trisulfapyrimidines. The wetting solution was cultured but failed to grow organisms. However, the soft contact lens culture grew *P aeruginosa*, as well as a *Bacillus* species and *Staphylococcus epidermidis*.

During the next week, the frequency of the gentamicin and Neosporin drops was decreased, the subconjunctival gentamicin was repeated once, the methicillin was not repeated subconjunctivally, and a regimen of 1% prednisolone acetate was started topically three times each day.

The corneal ulceration and anterior segment inflammation improved so that on Aug 12, 1976 she was discharged. When the eye was finally quiet, and the cornea epithelialized, she was left with a large scar and corneal thinning so that on her last visit, Feb 17, 1977, her visual acuity was counting fingers at 90 cm (Fig 4). In the meantime, she was given a pair of eyeglasses and instructed not to wear her contact lenses again. She has not decided whether to undergo a penetrating keratoplasty.

CASE 3.—A 19-year-old woman had worn −4.50 "P" series lens on the right eye and a −5.00 "P" series lens on the left eye for approximately five months. She had worn them, as directed, and she claimed that she sterilized them properly on a daily basis. On July 24, 1976, she awoke with photophobia and a foreign body sensation in the left eye. She placed her contact lens on the eye, which made it feel somewhat better. She wore the lens one day, but an increase in photophobia, pain, and redness prompted her to discontinue wearing it. The patient was referred to an ophthalmologist, who diagnosed a corneal ulcer, cultured it, and hospitalized her. She was treated for two days with topical Neosporin every hour, 30% topical sulfacetamide every hour, sulfisoxazole (Gantrisin) diolamine ointment four times each day, atropine ointment twice each day, and oral dicloxacillin sodium (250 mg) four times each day. The culture grew *P multophilia*. The organism was sensitive to carbenicillin, chloramphenicol, colistin sulfate, gentamicin, kanamycin, polymyxin B, and sulfisoxazole.

The patient was seen in consultation on July 27, 1976, when the corneal ulcer had become worse. There was a large, central epithelial defect that encompassed more than half of the central cornea. The cornea was thinned to half of its thickness, and there was gross purulent exudate adherent to the base of the ulcer and in the cul-de-sac. There was 4+ conjunctival and episcleral injection, and the palpebral conjunctiva exhibited 4+ papillae. The visual acuity was 6/7. 5 OD and counting fingers at 90 cm OS. The anterior chamber was filled to half of its depth with a hypopyon. There were tender, left preauricular and left submandibular lymph nodes. She was afebrile. Gentamicin sulfate (20 mg) was given subconjunctivally, topical Neosporin and sulfacetamide were continued, and therapy was started with 10% phenylephrine hydrochloride added to the topical atropine to dilate the pupil.

During the next four days, the infiltrate decreased, the ulcer became smaller, and the hypopyon resolved. Demeclocycline (Oral Declomycin) hydrochloride was discontinued. The regimen of sulfacetamide ointment, Neosporin, and sulfacetamide were continued.

She was discharged on July 31, 1976, with a 1-mm, central epithelial defect and markedly less infiltrate. During the next six weeks, the medications were tapered as the corneal inflammatory response and anterior chamber reaction became less.

On Sept 22, 1976, she reported to the office with pain and photophobia. A corneal erosion was present over the ulcer. This was successfully treated with pressure patches and gentamicin ophthalmic ointment.

By Nov 12, 1976, the eye was quiet, and all medications had been tapered off. On Jan 5, 1977, examination showed a quiet eye that was not being treated with any medications with a large, central corneal scar thinned to half of its thickness. The

Fig 1.—Pseudomonas corneal ulcer in case 1 on admission. Note extensive necrotic, infiltrative, and edematous cornea and hypopyon.

Fig 2.—Residual corneal scarring in case 1. Visual acuity was 6/120. Patient awaiting penetrating keratoplasty.

best corrected visual acuity was 6/120. She will undergo penetrating keratoplasty during the summer of 1977 after school is finished.

CASE 4.—A 18-year-old girl had worn −6.00 "B" series soft contact lenses in each eye uneventfully for four months. The lenses had been sterilized daily. Two days prior to being seen, she had awakened with pain and photophobia OD. She wore the lens for one day but then stopped wearing it because of pain. At that time she said her eye was red, and she noticed a white spot on her cornea. She was seen by her optometrist, who referred her for examination of her corneal disorder.

On examination, the visual acuity was 6/9 OD and 6/6 OS with −4.00 sphere. There was 1+ edema of the right upper lid. No foreign bodies were present in the upper or lower cul-de-sac, and 2+ papillae were present. The bulbar conjunctiva was 2+ injected, especially superotemporally. In that quadrant, there was a 3-mm. epithelial defect with punctate erosions surrounding it. A grayish-white subepithelial plaque densely surrounded by anterior stromal inflammatory cells was present. The anterior chamber exhibited 1+ flare and cells, and the pupil was miotic. The results of the remainder of the ocular examination of both eyes were normal.

The patient was admitted to the hospital, and scraping of the lesion was performed. No organisms were seen on Gram's and

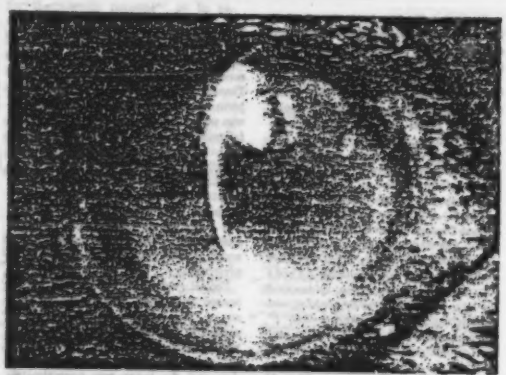

Fig 3.—Large corneal ulcer in case 2, on admission, surrounded by heavy infiltration and edema due to *Pseudomonas*. Heavy anterior chamber response with hypopyon.

Giemsa's stains. Cultures and sensitivity studies were performed for bacteria and fungi. Therapy was started with gentamicin and Neosporin every two hours around the clock and 1% atropine sulfate twice each day.

In two days, the lesion was epithelialized. The inflammatory response was unchanged. Dexamethasone (Maxidex) therapy was started twice each day and increased to four times each day during the next two days. The inflammatory cells decreased.

The culture grew *Escherichia coli* which

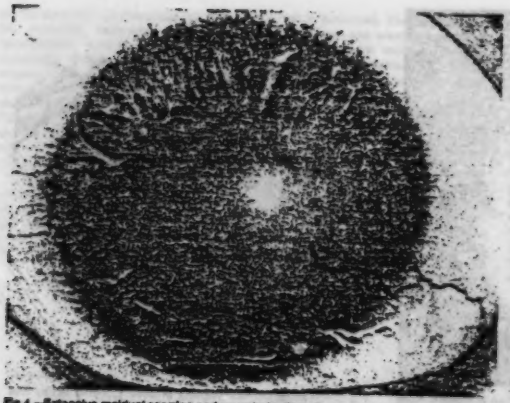

Fig 4.—Extensive residual scarring and vascularization of cornea in case 2. Visual acuity was counting fingers at 90 cm.

was sensitive to ampicillin, carbenicillin, chloramphenicol, colistin, gentamicin, kanamycin, nitrofurantoin, and polymyxin B.

On the fourth day, she was discharged. The medications were tapered and discontinued during the ensuing three weeks. Presently, she is not receiving any medications, visual acuity is 6/6 with a new, soft contact lens, and a small anterior scar persists superotemporally. She has been very carefully followed up, and after seven months she has had no problems.

CASE 5.—A 26-year-old man was seen at Firman Desloge Hospital, St Louis University on Aug 27, 1976, with a history of pain, photophobia, and tearing in his right eye for 24 hours. Two days previously, he had a scratchy, irritative sensation; he removed the lens, cleared his eye by blinking, and replaced the lens. He had worn a −3.00 "T" series cosmetic soft contact lens on each eye for approximately two years. He had sterilized the lenses only once every one or two weeks. He wore the lenses 15 to 18 hours each day.

The patient was seen in the emergency room where his visual acuity was reported as 6/45 OD and 6/9 OS. There was a peripheral superonasal corneal ulceration that measured approximately 3 × 3 mm on the right eye. The ulcer was surrounded by a dense accumulation of inflammatory cells. There was 1+ flare and cells in the anterior chamber, and the pupil was slightly miotic. The bulbar conjunctiva was 1+ injected, and a ciliary flush was present. The ulcer bed and margins were scraped with Kimura's spatula. Gram's stains were negative. Cultures were begun. Therapy was started with topical Neosporin every three hours by the resident, who was on call. The patient was seen the following day by one of us (J.J.P).

At that time, the ulcer was as previously described and Gram's stain, prepared on admission, was read as containing Gram-negative rods. The culture from the corneal scrapings later grew *P aeruginosa* which was sensitive to carbenicillin, colistin, sulfisoxazole, gentamicin, neomycin, polymyxin B, tobramycin sulfate, and trimethoprim/sulfa.

Topical gentamicin sulfate was administered every two hours while he was awake, and gentamicin ointment was applied at bedtime. Therapy was started with 0.25% scopolamine hydrochloride twice each day. He was seen the following day, and the lesion was approximately 50% epithelialized. During the ensuing two days, the lesion became totally epithelialized, and the stromal inflammatory cells began to decrease.

The gentamicin therapy was gradually tapered and eventually stopped after three weeks. The ulcer was completely healed, and the visual acuity was 6/6 in the right eye. The patient was refit with a new, cosmetic soft contact lens one month after the ulcer healed, and the inflammatory process had subsided. He has been closely followed up for six months without difficulties.

COMMENT

In 1976, Freedman and Sugar[1] made what seems to be the only case documentation of a culturally proved bacterial corneal ulcer in a patient who wore soft contact lenses for cosmetic or refractive purposes. Their patient developed bilateral *P aeruginosa* corneal ulcers that rapidly responded to intensive antibiotics with resulting 6/6 visual acuity OU. There have been previously reported cases of keratitis, in which corneal cultures were either not performed or not mentioned.[2-7] The outcome was good in all three patients who were described in the latter two reports.

In contrast, three of the five patients in our report suffered severe ulceration with resulting scarring and vascularization. The visual acuity after resolution of the active infection and inflammation was 6/120, counting fingers at 90 cm, and 6/120 in cases 1, 2, and 3, respectively. Two of these three patients are scheduled for penetrating keratoplasty. Cases 4 and 5 are of the less severe form. Their final outcome was minimal scarring with 6/6 visual acuity.

In the study by Freedman and Sugar,[1] culturally proved bacterial corneal ulcers developed in six patients who wore the same commercial, cosmetic soft contact lenses as our five patients. Five of the six (not case 5 of our series) claimed to have sterilized their lenses by boiling them daily in normal saline solution. None of the six prepared fresh saline solution daily. On the basis of the history given to us by our five patients, with the exception of patient 5 who only sterilized the lenses once a week, the patients' wearing and lens handling habits were probably not different from the vast majority of patients who wear soft contact lenses.

Why, then, did they suffer the serious complication of bacterial corneal ulcers when others do not? Obviously, that question cannot be answered by this report. We can only discuss possible weaknesses in lens management and possible sources of

bacterial contamination. Foreign bodies beneath the lens were never identified but could not be ruled out.

Perhaps there were errors in lens management that the patients did not report to us or even realize. We did not ask the patients to demonstrate the way they handled their soft lenses in terms of hygiene and sterilization techniques. The saline solution used for sterilization should be prepared fresh daily. None of the patients in our series followed that instruction. If the same saline solution is used as a wetting agent prior to insertion of the lenses, it could serve as a source of the organisms. In case 2, we cultured the patient's saline solution and found no bacterial growth. Cultures were not performed on saline solutions of the other four.

Laboratory studies to determine the adequacy of the recommended sterilization procedure for cosmetic soft contact lenses have shown the method to be effective.[4] However, the patient's actual routine sterilization procedure might be less than effective. To test that possibility, Bernstein et al[2] cultured the lens cases of patients who claimed they sterilized their lenses daily. They found that if cultures were taken immediately on opening the cases, 11 (44%) out of 25 were positive. They did not specifically state the organisms isolated in these instances but did mention the predominance of Gram-negative organisms, including *Pseudomonas* and *E coli*.

While it might be true that laboratory studies show that boiled lenses removed in sterile conditions under a laminar flow hood are free from bacterial growth, what really matters is the adequacy of sterilization in clinical usage. There are countless possible sources of contamination, such as the following examples: (1) failure to reach sterilization temperatures; (2) lens contact lens containers that might soak bacteria in while cooling; (3) contaminated rinsing or wetting solutions; (4) possible changes in lens surface characteristics with aging of the lens, which might make sterilization more difficult; and (5) contamination from skin. More studies like the one by Bernstein et al[2] should be performed to establish the frequency of contamination.

Cases of bacterial corneal ulcers in patients, who were soft contact lenses for therapeutic reasons[5-7] or in patients who were hard contact lenses,[8-10] have been documented. We have also seen these complications and suspect that there are many more unreported cases.

The prevention of bacterial corneal ulcers in soft contact lens wearers is difficult to determine, without knowing the source of contamination. We can only recommend strict adherence to the manufacturer's sterilization and handling procedures. Patients who wear the lenses must be carefully followed up and instructed to report unusual problems to their physician. A red, painful eye, especially with a "white spot," could indicate a bacterial corneal ulcer. Sudden persistent foreign body sensation while the patient wears the lenses can be the first symptom of bacterial keratitis.

Soft contact lenses, as well as hard contact lenses, have provided a pleasant alternative to spectacles for millions of patients. However, because lenses are ocular foreign bodies, they represent, at their best, a state of subclinical disturbance in normal physiology and, at their worst, a threat to visual acuity or even the loss of an eye. This communication was not written to discourage their use. Instead, it was written to remind those of us who fit contact lenses that the possibility of a serious bacterial ulcer is a real one.

S. Wolfe, MD, M. Allen, MD, P. Lembo, MD, and William Chrisman, MD, referred patients 1 to 4, respectively, to us for examination.

Nonproprietary Names and Trademarks of Drugs

Dicrocillin sodium—*Dyrill, Dynapen, Pathocil, Veracillin.*
Gentamicin sulfate—*Garamycin.*
Vancomycin hydrochloride—*Vancocin Hydrochloride.*

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changes of saline. To be on the safe side, you might want to ask your practitioner to "purge" your lenses for you.

Tips for lens wearers

- Even if your lenses feel comfortable, do not wear them longer than is normal or prescribed. This is crucial to long-term acclimation with contacts. "Overwear syndrome" is the most common cause of serious contact-lens problems. Typically, the full impact is not felt until several hours after removal of the lenses. Then there may be a sharp pain in the eye, severe watering, and an inflamed eyeball. If you experience these symptoms, consult a doctor immediately.
- Be alert for other signs that contact lenses may be causing you problems—red or painful eyes, a sudden change in vision, repeated irritation of the eye, copious secretions from the eye, or "spectacle blur" lasting more than 24 hours. (Spectacle blur, normally a passing phenomenon, occurs when lens wearers switch from contacts to glasses, especially if they wear hard lenses.) Any of these calls for a visit to your practitioner.
- To avoid discomfort, don't put your lenses in immediately after waking up. Corneas are generally swollen slightly from a night spent mostly closed off from the air. Wait about 30 minutes, the corneas will return to their normal shape.
- Incomplete blinking—with resulting poor tear flow under the lens—is a common cause of blurred vision and red, dry, burning eyes. To ease the discomfort, blink fully so that the lens moves slightly. Hold the eyes closed consciously for a second or two. A consistently strong blink can be developed through practice and can greatly help those who have difficulty tolerating contact lenses.
- Cosmetics can cause a variety of lens problems. It's very important to wash your hands and rinse them thoroughly before handling your lenses. However, avoid soaps that contain either deodorants or cold cream; they leave a film on the hands that can dirty lenses and irritate the eyes. Also avoid using hair spray when wearing contacts: mist spray is impossible to remove from a soft lens and can irritate the eyes of any lens user.
- Always insert contact lenses before applying makeup. Foundation or powder base—whether liquid, cream, or powder—is difficult to wash off the hands completely. Avoid all makeup containing "glitter"; the particles can irritate the eye and become embedded in soft lenses.
- If you use mascara, buy a new one and brush three or four times a year. Mascara commonly becomes contaminated with bacteria, which can start a corneal infection if the eye is abraded.
- Baseball players, tennis players, and others who must stare intently at a ball should consider soft lenses. Hard lenses don't cover the cornea completely. When they drift down the cornea between blinks, the edges may blur vision at a crucial moment. The wider diameter of soft lenses offer an advantage.

The controversy over salt tablets

Dissatisfaction is one of the daily nuisances and expenses of wearing soft lenses. With least dissatisfaction, much of that cost is for the saline solution used in rinsing, disinfecting, and soaking the lenses. Until a few years ago, a million or more soft-lens wearers were mixing one Bausch & Lomb salt tablet with one ounce of distilled water to prepare a batch of saline solution to use each day. Cost: about $10 a year for tablets and water.

In a July 1977 letter to practitioners, Bausch & Lomb touted salt tablets as "safe, effective, economical, and convenient." But, in November 1978, the company doubled to stop marketing salt tablets. Consumers were forced to buy bottles of premixed, preserved saline sold by Bausch & Lomb and other companies. Cost: about $70 a year, or 300 percent more than the cost of tablet-made saline. What's more, the preservative in the premixed solutions (thimerosal) causes eye irritation in about 10 percent of users. Preservative-free saline is also available, but it can cost as much as $140 a year.

The removal of salt tablets from the market enraged many consumers. They wrote angry letters to Bausch & Lomb (and to CU) charging that the company stopped marketing the tablets because its preserved saline was more profitable. But it wasn't as simple as that. Bausch & Lomb's switch was triggered, in part at least, by the Government's concern over the use of salt tablets.

FDA officials contended that salt-less wearers were misusing the tablets in several ways. They used the wrong kind of water; the saline they made up was often too salty or not salty enough for the eyes; and most important, their distilled water was often contaminated with bacteria, which could infect the eye. Since salt tablets contained no preservatives, bacteria could multiply in contaminated water used to make saline. A contact lens soaked in this saline could transmit bacteria to the cornea, and an abrasion could then allow bacteria to penetrate the cornea and cause a serious infection.

FDA officials acknowledged that daily use of a heating unit would kill all types of bacteria and eliminate any risk from contaminated saline. But they contended that many people didn't use their heating units every day. To support their argument, officials could point to about 30 cases in which corneal infections among salt-tablet users could be traced to contaminated saline. (Some infections, however, had also occurred with preserved saline.)

It was this line of reasoning that led to a letter, dated May 13, 1978, from David Link, director of the FDA's Bureau of Medical Devices, to Bausch & Lomb. He wrote: "FDA would appreciate communication from you to develop a schedule with you for the immediate withdrawal of the salt tablets from the marketplace." Six months later, Bausch & Lomb removed salt tablets from the market, although Link now says the FDA "did not order the removal of salt tablets."

An FDA advisory panel, however, has not been convinced that salt tablets are dangerous. Earlier this year it recommended that salt tablets be allowed on the market, provided that future studies show they are safe to use.

CU's consultants also believe that salt tablets can be used safely. What's more, they point out, the tablets are nonirritating and are the least expensive source of saline. Along with many other practitioners, our consultants are advising patients that they can use other salt tablets now on the market, provided they take the following precautions:

1. Use only distilled water or purified water labeled U.S.P. (United States Pharmacopeia). Tap water, and even "demineralized" or "deionized" water, may contain minerals such as iron or calcium that can cause problems. Keep the water refrigerated to reduce bacterial growth.
2. Use only U.S.P. salt tablets. Others, such as those used for heat exhaustion, may contain added chemicals. Companies making U.S.P. tablets include Blaine Laboratories Inc., Martin Industries, and Eli Lilly Co. Mix one ounce of distilled water with each 850-milligram salt tablet (or four ounces of water with the 3400-milligram Eli Lilly tablet).
3. Make a fresh batch of saline solution each day. Never re-use solution. And never use leftover saline solution to moisten the eyes or the lens.
4. Keep the vial in which the solution is prepared scrupulously clean. Rinse it daily with hot tap water.
5. Use the heating unit each time you take your lenses out. (It's the heating unit, not the saline, that disinfects.)
6. If lenses have not been worn for a week or more, add fresh saline and disinfect again before wearing them.

211

PERSONALLY SUBMITTED BY

BAUSCH & LOMB OPTICAL CENTER · 1400 NORTH GOODMAN STREET · ROCHESTER, NEW YORK 14602

WILLIAM F. GOODWIN
VICE PRESIDENT AND TECHNICAL DIRECTOR
OPTICAL DIVISION
(716) 338-6210

ALAN H. KOPLAN

SUPPL NEW CORRES

December 9, 1976

M.L.Gibson, M.D.
Food and Drug Administration
Division of Anti-Infective Drug Products
5600 Fishers Lane
Rockville, MD 20852

Dear Dr. Gibson: RE: NDA 16-895

The attached labeling for Bausch & Lomb sterile preserved saline solution is submitted in conformity with our discussion on December 9, 1976 with Mrs. Mary Brush and Dr. A. Scafidi.

We are also submitting at this time a letter from Mr. James P. Dodd, V.P. Bausch & Lomb, Inc., containing the commitment requested at the meeting.

Very truly yours,

William F Goodwin

AK/SM
Enc.

RECEIVED
DEC 9 1976
HFD-140
BUREAU OF DRUGS

BAUSCH & LOMB

December 9, 1976

Marie L. Gibson, M.D.
Director, Division of Anti-Infective Drug Products
Food and Drug Administration
5600 Fisher's Lane
Rockville, Maryland 20852

RE: NDA 16-495

Dear Dr. Gibson:

This letter will constitute a commitment by Bausch & Lomb that upon approval of the sterile preserved saline supplement to the above referenced NDA, a plan will be implemented to phase out distribution of BOYLINE® sale tablets. Once adequate supplies of the saline solution are available in retail outlets, we will discontinue all domestic sale of the tablets.

We further commit that upon approval of the supplement we will act expeditiously to initiate distribution of the saline solution.

Sincerely,

James P. Dodd
Vice President

JPD:jpw

GARDNER (F)

July 19, 1976

MEDICAL OFFICER'S REVIEW OF ANNUAL REPORT ON NDA 14-895

Sponsor: Bausch & Lomb
1400 N. Goodman St.
Rochester, New York 14602

I. Name of Product: A. Trade Name: Soflens Contact Lens

B. Generic Name: Polymacon Hydrophilic Contact Lens

II. Annual Progress Report A-MR for the Period from March 1975 to February 1976.

A. Clinical Data: There are final reports from 10 clinical studies included in this submission. There are additional 8 proposed clinical studies submitted. All the studies have been reviewed and revealed nothing new or unremarkable. The only one suggestion I would have for change in package insert if it was thought necessary is that persons wearing the lenses to sky dive should wear goggles when doing so.

B. Adverse Reactions: There are 86 adverse reactions reported. Just about every conceivable problem that has been involved with contact lenses has been reported. Since there are so many different types of lenses I do not feel analysis would be reasonable.

C. Labeling: The package insert&labels for the varied types of lenses, patient instruction and clinician fitting manuals have all been reviewed and appear satisfactory.

D. Distribution: There were a total 2,903,016 lenses shipped.

III. Evaluation: Evaluation of this entire annual review reveals that further stress should be placed on proper care and disinfection of the lenses. It should be emphesized that careful scrutiny on the part of the clinician should be undertaken before patient is fitted with these lenses. The 86 adverse reactions revealed bacterial ulcers, mycotic ulcers, as well as viral ulcers. Allergy and scleritis along with intracorneal hemorrhages are also reported. Corneal melting with sequelae has also been reported. Numerous other problems such as errosion, staining, keratitis, abrasions, neovascularization, infiltrates, allergy, pannus, pterygion, corneal nebulae and palpebral lesion are also reported.

IV. Recommendation: Considering the number of lenses dispensed in this country (1,915,294) I feel the incidence of adverse reactions is low but must be carefully monitored.

A. F. Scaffidi, M.D.
Division of Anti-Infective Drug Products

cc:
Orig NDA
HFD-108
HFD-140, HFD-140/C30
HFD-140/AFScaffidi:js 7/20/76

B. SUMMARY OF ADVERSE REACTIONS

March 1975-Feb. 1976

Name of Reaction	Report Returned	Total
Conjunctivitis	Recovered	8
Infectious	Recovered	1
	No followup*	1
Erosions	Recovered	2
Injection	Recovered	5
Keratoconjunctivits	Recovered	3
Ulcer	Recovered	2
Ulcer (Mycotic)	Recovered	1
Ulcer (herpes Simplex)	Recovered	1
Ulcer (Bacterial)	Alive with Sequelae	1
	Recovered	1
Ulcer (Unknown)	Recovered	5
Staining	Recovered	5
Keratitis	Still under treatment	1
	Recovered	4
Abrasions	Recovered	12
Infiltrates	Still under Treatment	1
	No answer from physician	1
Neovascularization	Recovered	8
	Alive with Sequelae	2
	No reply	1
	Still under Treatment	1
Edema	Recovered	5
Intracorneal Hemorrhage	Recovered	1
Allergy	Still under Treatment	1
Scleritis	Recovered	1

*practitioner did not supply final report

VI. Distribution

A. The following is the summary of Production, Inventory and Lens Distribution.

Shipments	
Lenses Shipped to Practitioner	1,915,294
Lenses Shipped Export	387,722
TOTAL LENSES SHIPPED	2,303,016
Production and Inventory	
Initial Inventory	563,915
Lenses Produced (Net) in Period	2,621,008
Return from Customer	128,641
TOTAL LENSES AVAILABLE	3,313,564
Less Lenses Shipped	2,303,016
Less Lenses Used in Plant	247,691
FINAL INVENTORY	762,857
Lenses Distributed in New York State	172,376
Lenses Shipped in Interstate Commerce (Domestic)	1,742,918
TOTAL LENSES SHIPPED	1,915,294

Name of Reaction	Reports Returned	Total
Palpebral Lesion	Recovered	1
Pannus	Recovered	1
Pterygian	Still under Treatment	1
Corneal Nebulae	Alive with Sequelae	1
Corneal Molding	Recovered	2
	Alive with Sequelae	1
Pseudomonas	Alive with Sequelae	3

DEPARTMENT OF HEALTH, EDUCATION, & WELFARE
PUBLIC HEALTH SERVICE

SUPPLEMENTAL AGREEMENT (OMH)

CONTRACT NO.	PAGE 1 OF 1 PAGES
223-76-3018 C	GARDNER
MODIFICATION NO.	EFFECTIVE DATE
1	SEP 28 1977 (6)

CONTRACTOR (Name and Address)
University of Arkansas
4301 West Markham Street
Little Rock, Arkansas 72201

ISSUING OFFICE
HEW/Public Health Service
Food & Drug Administration, HFA-512
5600 Fishers Lane, Room 5B-19
Rockville, Maryland 20857

ACCOUNTING AND APPROPRIATION DATA
AMOUNT OBLIGATED: $63,223.00
(Cost Sharing - See Article IV)
Appropriation: 7570600
Allot. Symbol: 7-6992214-D-04017 ($41,201) PMS 22320H-20
Allot. Symbol: 7-6994112-M-7007 ($22,022) PMS 223501-10 0 C 25 31

Upon the effective date of this Modification, the subject contract is amended as follows:

1. The amount on the face of the contract is hereby changed from $49,595.00 by $74,398.00 to $123,993.00.

2. The expiration date on the face of the contract is hereby changed from June 28, 1977 to June 28, 1978.

3. Article I entitled, "Scope of Work," is hereby amended to include the following:

Paragraph A is hereby amended to add the following Item (3):

(3) Develop and coordinate a reporting system to obtain information concerning the possible problems associated with the use of contact (soft and hard) and intraocular lenses from opthalmologists, other physicians and optometrists.

Except as hereby modified, all terms and conditions of said contract remain unchanged and in full force and effect. This Supplemental Agreement is entered into pursuant to the authority of Section 302(c)(5) of the Act, 41 USC 252(c)(5).

BOARD OF TRUSTEES
UNIVERSITY OF ARKANSAS
NAME OF CONTRACTOR

BY Charles E. Bishop
SIGNATURE OF AUTHORIZED INDIVIDUAL

Charles E. Bishop
TYPED NAME

TITLE President

9/22/77
DATE

UNITED STATES OF AMERICA

BY Ira R. Marshall Jr.
SIGNATURE OF CONTRACTING OFFICER

Ira R. Marshall, Jr.
TYPED NAME

September 29, 1977
DATE

PHS-4910-4 (REV. 7/67)

Paragraph B is hereby amended to add the following Item (4) and (5):

(4) Solicit the reporting of contact (soft and hard) and intraocular lenses through appropriate journal advertising.

(5) Collect and tabulate data concerning the occurrence, nature and severity of complications associated with the use of contact (soft and hard) and intraocular lenses. All information received on these events that is received by the FDA will be furnished to the contractor on a computer print-out. No data will be released that is not in compliance with the Freedom of Information Act. The data will be supplied to the contractor no later than fourteen (14) days after the quarter has ended.

4. Article II entitled, "Period of Performance," is hereby changed from June 28, 1977 to June 28, 1978.

5. Article III entitled, "Reports," is hereby amended as follows:

a. Paragraph "E" is hereby superseded by the following paragraph "E".

E. All reports shall be delivered to:

Department of Health, Education, and Welfare
Food and Drug Administration
Negotiated Contracts Branch, HFA-512
5600 Fishers Lane, Room 5B-19
Rockville, Maryland 20857

The Contractor shall mark each shipment with its company name, contract number, item number, and quantity (indicate partial or final shipment).

5/15/78

GARDNER (H)

NDA 16-895

Bausch and Lomb
Soflens Division
Attention: Mr. William F. Coombs
635 St. Paul Street
Rochester, New York 14602

Dear Mr. Coombs:

In a number of recent meetings with you, particularly regarding the use of marketed approved preserved saline solutions (marketed by other manufacturers) for use with the Bausch and Lomb Soflens contact lens, representatives of the Division of Anti-Infective Drug Products have discussed the continued marketing of salt tablets for heat disinfection of contact lenses.

Needless to say, we recognize that the use of patient prepared saline was approved at a point in the history of contact lens regulation when our understanding of the uptake and binding of preservatives was new information. Many patients have used the system of preparing saline with salt tablets apparently without ill effects. However, the second and every subsequent lens approved has been approved only with the use of sterile preserved saline in multi-use containers for heat disinfection.

The history of salt tablet use has shown us a number of difficulties:

1. Even though instructions require daily preparation and disposal of saline, this is not always done. When the saline is prepared at irregular intervals, the risk of microbial growth is magnified since there is no preservative. If such contaminated solutions are used, contrary to directions, to rinse lenses or to lubricate the lens, the results may be disastrous. This potential has been recently realized and documented in an article, Bacterial Corneal Ulcers in Cosmetic Soft Contact Lens Wearers, Krachmer, J.H. and Purcell, J.J., Arch. Ophthalmol., Jan. 1978: 57-61.

2. Frequently, the saline is mis-prepared resulting in either a hypotonic or hypertonic lens with the appropriate difficulties. Please refer to the human clinical effects reported from the use of non-isotonic saline showing irreversible corneal thickening in animals and similar effects in humans. (Attached)

3. If water other than the recommended distilled water is used, unacceptable deposits may result.

Mrs. Bruch of the Division of Anti-Infective Drug Products has enumerated these difficulties with salt tablets in several public forums both for the American Optometric Foundation and for the Contact Lens Association of Ophthalmologists.

Our desire to have preserved saline solutions available as an replacement for salt tablets for Bausch and Lomb lenses has been discussed with you on a number of occasions. We note that Mr. Dodd (letter dated December 9, 1976) also committed Bausch and Lomb to removal of the salt tablets when saline solution was available to them.

Preserved saline solution manufacturers have assured us that the production capacity required for Bausch and Lomb wearers and new fittings is available with presently approved solutions. There has been no reason in the past and none has been put forth since these products have been labeled for Bausch and Lomb lenses to indicate any problem with the use of marketed saline solutions.

The recent article (Arch. Ophthalmol, January, 1978) discussing 5 cases of corneal ulcers points to the misuse of saline with the patients failure to make fresh saline each day as a critical defect in a regimen using unpreserved solutions. If water solutions are used, allowed to stand and are unpreserved, the only expectation considered by microbiologists will be that gram negative organisms, particularly Pseudomonas, will grow. Patients can be expected to escape serious infection for some time but as in the cases reported, they are flirting with a dangerous situation, particularly if the cornea is accidently abraded. The patient may be even more likely to use non-sterile saline if there is some discomfort after applying the lens.

Representatives of Bausch and Lomb have argued that increased cost will influence patients to use unapproved materials. Certainly preserved, prepared saline is more convenient and cost cannot become a consideration where safety to the patient and continuing risk are involved.

FDA would appreciate communication from you to develop a schedule with you for the immediate withdrawl of the salt tablets from the marketplace.

Sincerely yours,

David M. Link, Director
Bureau of Medical Devices

cc:
Orig HDA
HFK-1
HFD-100
HFD-140
HFD-140/Joyce
HFD-140/Scafidi
HFD-140/MKBruch:
llb-5/1/78

68-598 O—80——3

GARDNER (H)

July 1978 - June 1979 - Contact lens solutions

DRUG	REACTION	DAILY DOSE	UNITS	DOSAGE FORM	ROUTE ADM.	AGE	SEX	DURATION THERAPY (DAYS)	OTHER DRUGS	NO. OF PATIENTS	REF.
Acetazolamide	Pancytopenia, Death	1	gm	--	SYST	66	M	105	1	1	1.
Acetazolamide	Aplastic anemia, Death	1	gm	--	SYST	66	M	123	2	1	2.
Acetazolamide	Thrombocytopenia, Leukopenia, Aplastic anemia	--	--	--	SYST	--	--	--	--	--	3.
Acetazolamide	Agranulocytosis	250	mg	tab	PO	66	F	--	1	1	4.
Acetazolamide	Aplastic anemia	750	mg	tab	PO	84	M	210	2	1	5.
Acetazolamide	Aplastic anemia	--	--	--	SYST	--	--	--	--	--	6.
Acetazolamide	Aplastic anemia, Death	500	mg	tab	PO	72	M	--	--	1	7.
Acetazolamide	Renal calculi	--	--	--	SYST	--	--	--	--	1	8.
Acetazolamide	Generalized rash	250	mg	tab	PO	74	F	--	0	1	9.
Adapettes	White central deposit clouding soft contact lens	24-48	?	dps	OPH	12	F	300	0	1	10.
Adapettes	Prolonged mydriasis and discomfort	6-8	--	dps	OPH	53	F	1	1	1	11.

FAST PAGE OR NUMEROUS PAGES

* Acute t - ?

GARDNER (G)

NATIONAL REGISTRY
OF DRUG INDUCED OCULAR SIDE EFFECTS

F. T. Fraunfelder, M.D.
Executive Director
Martha Meyer
Associate Director

May 13, 1980

Bob Eckhardt, Chairman
Subcommittee on Oversight and Investigations
Committee on Interstate and Foreign Commerce
House of Representatives
Washington, D.C. 20515

Dear Mr. Eckhardt:

The information on hard and soft contact lens solutions and soft contact lenses is enclosed. Although the exact date of each entry is not shown, one can determine the year in which each case was received. In April, 1978, the National Registry of Drug-Induced Ocular Side Effects did a special study for the FDA Bureau of Devices. A national mailing was sent to ophthalmologists and optometrists specifically asking for possible adverse effects from soft or hard contact lenses and various contact lens solutions.

Because of the numerous requests for information made of the Registry, we have never attempted to keep a log of such requests. We answer all requests from consumers, physicians and public agencies.

Best wishes.

F. T. Fraunfelder M.D.

F.T. Fraunfelder, M.D.
Executive Director

FTF/cl
Enclosures

68 598 68

3181 S.W. Sam Jackson Park Rd. Portland, OR 97201 (503) 225-8456

July 1979 - June 1980 - Contact Lens Soln

DRUG	REACTION	DAILY DOSE	UNITS	DOSAGE FORM	ROUTE ADM.	AGE	SEX	DURATION THERAPY (DAYS)	OTHER DRUGS	NO. OF PTS.	REF
Adapettes	Corneal opacity, keratitis	--	--	Soln	OPH	22	M	2	--	1	1
Bausch & Lomb Saline Solution	Keratoconjunctivitis (OU)	--	--	--	OPH	19	F	--	0	1	2
Bausch & Lomb Saline Solution	Keratoconjunctivitis (OU)	--	--	--	OPH	--	--	--	--	2	3
Bausch & Lomb Soft Contact Lens Cleaner	Keratitis	--	--	--	OPH	--	--	--	--	7	4
Bausch & Lomb Soft Contact Lens Cleaner	Keratitis	--	--	--	OPH	32	F	--	1	1	5
Boil n Soak	Eye irritation	--	--	--	OPH	--	--	90	0	2	6
Boil n Soak	Irritated red eyes	--	--	--	OPH	26	M	60	0	1	7
Boil n Soak	Irritated red eyes	--	--	--	OPH	26	F	60	0	1	8
Boil n Soak	Irritated red eyes	--	--	--	OPH	26	F	60	0	1	9
Enzymatic Soft Contact Lens Cleaner	Corneal lesion	--	--	--	OPH	--	M	--	--	1	10
Enzymatic Soft Contact Lens Cleaner	Amblyopia (3), glaucoma (1), keratoconjunctivitis (1), Keratitis (1), eye hemorrhage (1), eye disorder (1), ocular pain (2)	--	--	--	OPH	--	--	--	--	9	11

* Acute toxicity

DRUG	REACTION	DAILY DOSE	UNITS	DOSAGE FORM	ROUTE ADM.	AGE	SEX	DURATION THERAPY (DAYS)	OTHER DRUGS	NO. OF PTS.	REF
:nzymatic Soft :ontact Lens Cleaner	Eye irritation (OU) with non-boiled lenses	--	--	--	OPH	40	M	--	--	1	12
:nzymatic Soft :ontact Lens Cleaner	Marked burning, swelling, and moderate injection	--	--	--	OPH	30	F	1	0	1	13
'lexsol	Keratoconjunctivitis	--	--	Sol	OPH	--	--	3 - 17	1	2	14
lexsol	Ocular injection	--	--	--	OPH	--	--	--	--	--	15
lexsol	Allergic conjunctivitis	--	--	--	OPH	23	F	--	0	1	16
lexsol	Progressive reddening and irritation (OU), corneal/ conjunctival epithelial slough in area of contact	--	--	--	OPH	30	M	7	0	1	17
lexsol, normal	Irritation	--	--	--	OPH	16	F	--	--	1	18
eserine	Chemical conjunctivitis	--	--	dpe	OPH	51	M	60	--	1	19
eserine	Ocular injection	--	--	--	OPH	--	--	--	--	--	20
reflex	Keratitis	--	--	--	OPH	32	F	--	--	1	21
reflex	Keratitis	--	--	--	OPH	36	F	--	--	1	22

Acute toxicity

DRUG	REACTION	DAILY DOSE	UNITS	DOSAGE FORM	ROUTE ADM.	AGE	SEX	DURATION THERAPY (DAYS)	OTHER DRUGS	NO. OF PTS.	REF
Prefilex	Keratoconjunctivitis	--	--	--	OPH	--	--	--	0 - 1	2	23
Sodium chloride	Eye disorder, amblyopia	--	--	dps	OPH	0	F	--	--	1	24
Sodium chloride (with preservatives)	Allergic or irritative reaction	--	--	--	OPH	--	--	--	--	2*	25
Sodium Chloride Tablets	Corneal infections	--	--	--	OPH	--	--	--	--	196	26
Sodium Chloride Tablets	Pseudomonas aeruginosa keratitis	--	--	--	OPH	39	M	--	0	1	27
Sodium Chloride Tablets	Pseudomonas aeruginosa keratitis	--	--	--	OPH	19	M	--	0	1	28
Soft Contact Lens Cleaner (chemical)	Punctate keratopathy from adenovirus 8 (OU)	--	--	--	OPH	37	M	180	--	1	29
Soft-Mate	Keratoconjunctivitis, amblyopia	--	--	dps	OPH	22	F	--	1	1	30

1. Case Report #1865
2. Case Report #2228
3. Case Report #2228
4. Case Report #2245
5. Case Report #2245
6. Case Report #1865
7. Case Report #2242
8. Case Report #2242
9. Case Report #2242
10. Case Report #1865
11. Case Report #1865
12. Case Report #1867
13. Case Report #2244
14. Case Report #1865
15. Case Report #2049
16. Case Report #2052
17. Case Report #2241
18. Case Report #1868
19. Case Report #2043
20. Case Report #2049
21. Case Report #1571
22. Case Report #1572
23. Case Report #1865
24. Case Report #1865
25. Case Report #2187
26. Case Report #1810
27. Case Report #2151
28. Case Report #2152
29. Case Report #2172
30. Case Report #1865

* Acute toxicity

NATIONAL REGISTRY
OF DRUG INDUCED OCULAR SIDE EFFECTS

RECEIVED
MAY 2 6 1980
[illegible] COHNADT, M.D.

F.T. Fraunfelder, M.D.
Executive Director
Martha Meyer
Associate Director

[illegible] PAT 76 [illegible]

Please find a copy of case report #1810 enclosed.

M. Meyer

Martha Meyer

— UNIVERSITY OF OREGON HEALTH SCIENCES CENTER, 9181 S.W. Sam Jackson Park Road, Portland, OR 97201 (503) 225-8450 —

Sodium Chloride Tablets

GARDNER (K)

1910 QUICK UPDATE

I have here now 196 cases of corneal infections secondary to salt tablets. These have been documented by the doctor. All of these incidentally, the case and the lens as well as the patient's eye were cultured. Believe this or not 10 cases of Pseudomonas, 6 fungal infections, about 12 staphylococcal infections and just about all the rest of them are _____ except for two. There are two ~~Staph~~ streptococcus ulcers and these are an anaerobic bug. Of these infections 22 of them have now gone to corneal transplant. All these patients were using a salt tablet. None were using preserved saline.

DRAFT

CONTACT LENS SURVEY

Background

This report analyzes information associated with the use of hard and soft contact lenses.

Most of the data was obtained through a contract with the University of Arkansas's Department of Ophthalmology, FDA Contract No. 223-76-3018. A copy of the contract is provided as Attachment A.

The University of Arkansas contract was initially developed by the Bureau of Drugs (BD) to collect data on drug-induced ocular side effects. BD's contract was modified in 1977 to collect data on problems associated with the use of contact lenses and intraocular lenses (IOL's). However, shortly after the contract was negotiated, the modification was amended to remove IOL's from the study. IOL's were deleted from the device study to prevent a duplication of effort since the enactment of the Intraocular Lens Investigational Device Exemption made the reporting of IOL problems mandatory.

The contact lens contract required the University of Arkansas to collect data on problems associated with both contacts and IOL's by mailing a letter (which explains the purpose of the study) and reporting forms to ophthalmologists and optomologists. In addition, requests for support of the survey were conducted via "advertising" in appropriate medical journals. All reports were initially sent to the contractor who removed the physician's names. The reports were then sent to the Bureau of Medical Devices (BMD) for review.

During the review of the contact lens reports, two other sources were analyzed for any possible correllation: (1) the third quarter report of the registry for drug induced ocular side affects, and (2) information from the Device Experience Network (DEN).

Findings

The contact lens survey generated a total of 1,525 reports. However, only 762 of them involved adverse effects associated with contact lenses and/or solutions used with such lenses.

The data divides itself into two major categories: (1) hard, and (2) soft contact lenses, and six types of complications: (1) edema/irritation, (2) infection, keratitis/conjunctivitis, (4) ulcer/abcess/scarring, (4) vascularization, (5) lens care preparation problems, and (6) preservatives.

Before describing the data, it is important to note that there are some basic limitations associated with analyzing and interpreting the results of this study. The majority of this study's shortcomings can be attributed to the limitations of the form used to collect the information. Since the Bureau's effort was an "add on" to an existing contract, there was

insufficient time to obtain approval from OMB to develop and use a new form. Consequently, BD's Form 1629a - Drug Experience Report was used. This form is designed for reporting adverse drug reactions and was inadequate for the data being sought by the contact lens study.

The primary problems caused by the form's design are as follows:

a. A reporter would describe an event and a related complication and then state that the same type of problem had occurred with a certain percentage of his patients. This, of course, made it difficult to determine the actual number of individuals who experienced that particular problem.

b Reporters often mentioned a lens and solutions, described a problem but did not specify the actual cause of the complication. Although the nature of the complication and the description would often indicate that either the lens or the solution was involved, it was a difficult process. Therefore, there may be some unavoidable weighting of data in certain complaint categories.

c. Since the form does not provide for cumulative reporting, the figures will not add up to 100%.

In spite of the limitations of the data generated by the study the response was relatively good.

Major Findings

a. Approximately 81% of the 762 reports form the device study involved soft contact lenses; 19% involved hard lenses.

b. In terms of complications, the largest category was edema/irritation which represented 89% of all complaints. The largest category of causual factors was solutions (wetting, cleaning, sterilizing, etc.) which was mentioned in 93% of the reports.

A corollary point of interest is found in the National Drug Registry Report which indicates that, for a 3-month period there were 1,232 reactions to the solution categories which were represented by 26 different solutions. In this area, allergic reaction (edema/irritation) accounts for 60.7% and conjunctivitis accounts for 36.3%. Information from this report is tabulated as much as possible in Attachment B.

The DEN files have a total of 174 complaints involving contact lenses, and IOL's (prior to the IDE study) with the following statistics: 91 involve solutions, 40 involve soft contact lenses, 1 involves a soft contact lens sterilizer, and 42 involve IOL' .

those cases where a reporter specifically mentions preservatives they
ve been included as the primary source of the problem. The majority of
mplaints regarding the soft contact lenses are edema, irritation, or
dness (89%). In these cases a few solutions are primarily mentioned as
ing in use when the problems develop, and all these solutions contain
rious preservatives such as Thimerisol, EDTA, and chlorahexadine.
few reports indicated that the ophthalmologists believed that the material
the soft contact lens itself was causing the reaction.

is type of reaction could not be verified from the information obtained.
wever, the type of reaction was studied during the development of the
ses and although possible, is not considered to be significant. It is
so noted that oral contraceptives appear to cause problems with some
ntact lens users. (This information is also noted in the Product Information
ets for O.C. uses.) This reaction appears to affect those who use
th soft and hard lenses. However, this type of reaction is difficult
tabulate since it is often mentioned in conjunction with other types
problems. However, this problem should be fairly common since 66.4%
the wearers of contact lenses are women and the use of contact lenses
steadily increasing.

clusion

efinitive cause and effect relationship between contact lenses and the
blems noted in the reports is not possible due to the limitation of
data and the study. However, it is possible to point out some reasonable
ervations concerning contact lens use. For example, 81.1% of the
orts involve soft contact lenses; 88.9% of the complaints involve
ma and irritation, while 33% show infection, keritits, conjunctivitis,
; 72.3% of the complaints involve the solutions used to clean, soak,
rilize, or otherwise treat the contact lenses; and 20% of the complaints
directly concerned with the preservatives used in the solutions.
hough there is no effective way to judge the actual number of complaints
t these percentages represent, it does appear that there are problems
ociated with soft contact lens cleaning agents. Overall, the primary
blem seems related to the cleaning and sterilizing materials which are
essary for contact lens use and the methods in which they are used.
ergic reactions are much more common than anticipated, but human error
failure to follow instructions must be considered with this type of
duct. It is our speculation from analyzing the individual reports
t there are more complaints generated by the user due to poor technique
n can be attributed to the materials themselves. The reports seem to
icate that a thorough indoctrination by the optometrists concerning
methods of using contact lenses, keeping them clean, and the necessity
closely follow instructions (particularly in the procedure of rinsing
chemical solutions from the lenses after cleaning) is the best method
voiding these problems. Instructions and training may be initiated
the optometrists or physicians in their prescription of the lenses, or
require a review of the manufacturer's labeling to assure that proper
tructions are provided and that the importance of following them is
clear to the users. However, cleaning solutions are primarily over-
rcounter items. As such, user may purchase and switch them at will
lting in no great familiarity with any one brand. In addition, there
a number of products which have a relatively large number of complaints

associated with them and it may be necessary to review these products specifically to determine if their labeling is entirely adequate for an over-the-counter type product. The cleaning products most frequently mentioned are the Preflex, Flexol, and Normal cleaning solutions manufactured by Burton Parsons Co., Washington, D.C. These products are the subject of NDA's which indicate that they contain one or more preservatives, some contain three different items. All of these preservatives could cause allergic reactions, either singly or in consort. The preservatives are Thimerisol, EDTA, and Chlorahexadine. It is interesting to note when these solutions are indicated as being a cause of irritation and the patient returns to a solution of boiled plain salt water for cleansing his lenses, the original problems generally disappear.

As a result of the information received from the contact lens study, we recommend that the labeling of all products used to clean, soak, and wet, or otherwise treat contact lenses, both soft and hard, be reviewed for clarity and adequacy of the directions. We also believe that an educational program based on information contained in the labeling would be helpful to all contact lens users. Based upon the results of the labeling review, a Drug Bulletin or FDA consumer article should be considered to remind soft contact lens users of the importance of proper cleaning techniques.

Charles W. Gressle

Attachments:
Attachment A
Attachment B

Gardner (M)

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

: Chief, Biological Sciences Branch
Division of Ophthalmic, ENT and
Dental Devices (HFK-460)
Bureau of Medical Devices

DATE: April 18, 1980

M : Medical Officer
Division of Anti-infective Drug Products (HFD-140)

JECT: Notebook of Salt Tablet Adverse Reactions

Enclosed are data that I have personally collected from clinicians who have contacted me in the past. All these cases involve patients who were using salt tablets in conjunction with their hydrophilic contact lenses. I collected and kept this data because of my concern over the use of salt tablets. I will continue to collect this sort of data when I come in contact with clinicians.

A.F. Scafidi, M.D.

Scafidi

Adverse Events — SALT TABLETS - ONLY -

1. Corneal ulcer – cultured corn ker exp # antibiotics - cleared peripheral corn
2. Keratitis - cultured - Pseudomonas - # antibiotics - cleared no scar
3. Keratitis - cultured - no bug # antibiotics - cleared
4. Corneal ulcer - cultured pseudomonas – # antibiotics + transplant
5. Keratitis - cultured - staphylococcus - # antibiotics - cleared
6. Keratitis - cultured – no bug - # antibiotics - cleared
7. Corneal ulcer - cultured - Staph - cleared ± antibiotics
8. Keratitis - cultured - no bug Candida-Steroid Combo - cleared
9. Corneal ulcer - cultured - no bug - cleared ± antibiotics
10. Corneal ulcer – cultured - staph - # antibiotics - cleared
11. Bilateral fungal Keratitis - aspergillus - bilateral transplants after # 2 primonic
12. Keratitis - cultured - no bug - # antibiotics - cleared
13 Keratitis - cultured - no bug # antibiotics - cleared
14 Keratitis - cultured - no bug # antibiotics - cleared
15 Bilateral Keratitis - no bug on culture # antibiotics 12 weeks cleared – cleared after 3 weeks Rx
16. Keratitis - no bug on culture – # antibiotics – cleared
17. Keratitis - cultured - no bug # antibiotics – cleared
18. Keratitis - cultured - no bug # antibiotics - cleared
19. Keratitis - cultured - no bug # Candida - cleared
20 Bilateral Keratitis - cultured - Staphylococcus # antibiotics - cleared
21 Keratitis - cultured - no bug # antibiotics - cleared
22 Keratitis - cultured - no bug - cleared ± antibiotics - no comment on T-graft therapy
23 Corneal ulcer - cultured - staphylococcus - cleared ± antibiotics
24 Keratitis - cultured - no bug - cleared ± antibiotics
25 Keratitis - cultured - staphylococcus - cleared ± antibiotics
26 Keratitis - cultured - no bug - cleared ± antibiotics
27 Keratitis - OU # 2 gram stain culture - cleared ± antibiotics
28 Corneal ulcer - cultured staphylococcus – unsatisfactory transplant – decay finish
29 Corneal ulcer - Staph – # antibiotics peripheral keratoma
30 Keratitis cultured - no bug cleared ± antibiotics
31 Keratitis - cultured - staphylococcus cleared ± antibiotics

Keratitis –	culture – no org –	Rx antibiotics – cleared
Keratitis –	culture – diphtheroids	cleared c antibiotics
Central ulcer	culture – Pseudomonas	cleared c antibiotics
Keratitis –	no growth	cleared c antibiotics
Corneal ulcer	no growth	Rx antibiotics pregnant transferred
Keratitis	culture – diphtheroids	Rx antibiotics cleared
Keratitis	culture – no org	Rx antibiotics cleared
Keratitis	culture – no org	Rx antibiotics cleared
Corneal ulcer	culture – pseudomonas	cleared c antibiotics
Keratitis	no growth	Rx antibiotics – healed
Keratitis	culture – neg	Rx Combo – cleared
Keratitis	Culture – diphtheroids	Rx antibiotics – cleared
Keratitis	no growth	Rx antibiotics – healed
Corneal ulcer	culture – fusiform bacteria	antibiotics + transplant
Keratitis	neg culture	antibiotics – cleared
Keratitis	culture – Staph	antibiotics – cleared
Keratitis	no growth	Antibiotics – cleared
Keratitis	culture – neg	Combo – cleared
Corneal ulcer	Staph	Combo – cleared
Keratitis	no growth	Combo – cleared
Keratitis	culture – diphtheroids	antibiotics – healed
Keratitis	diphtheroids	antibiotics – cleared
Keratitis	no growth	antibiotics – cleared
Keratitis	culture – neg	Rx antibiotics – cleared
Keratitis	culture – neg	Rx Combo neg – cleared
Keratitis	culture – neg	Rx antibiotics – cleared
Corneal ulcer	culture – Staph	Rx antibiotics – fully transplant
Keratitis	culture – diphtheroids	Healed c antibiotics
Keratitis	culture – neg	Rx antibiotics – cleared
Keratitis –	Culture – neg	Rx antibiotics – no response switched to Steroid – no response after D/C all med + hosp. c NSR now – clear (x 3 days)
Corneal ulcer	culture – fungus	R Appendix B – transplant
Keratitis	culture – diphtheroids	Rx Steroids – no response Combo – cleared x days
Keratitis	no growth	Rx antibiotics – cleared

		adverse Reaction			
65	corneal ulcer	- control - culture	Pseudomonas	- R antibiotics - control bacteria cleared hospital 4 IVA 3 times	
66	Keratitis	- neg culture	-	R antibiotics - cleared	
67	Keratitis	- culture - staphylococcus		R antibiotics - cleared	
68	fungal ulcer	- culture aspergillus		R pimaricin - cleared + painful scar	
69	keratitis	- neg culture		R Combo - cleared	
70	Keratitis	culture - neg		Antibiotic R cleared	
71	Keratitis	culture - neg		R antibiotics - cleared	
72	Keratitis	culture - neg		R antibiotics - cleared	
73	Keratitis	culture - neg		antibiotics - cleared	
74	Keratitis	culture - staphylococcus		Combo - no response in 5 days combined to antibiotics cleared in 4 days	
75	Keratitis	culture - neg		R antibiotics - cleared	
76	Keratitis	neg culture		antibiotics - cleared	
77	Keratitis	culture - neg		antibiotics - cleared	
78	Keratitis	culture - neg		antibiotics - cleared	
79	Keratitis	neg - culture		R antibiotics - cleared	
80	Corneal ulcer - painful	Staph - positive		Antibiotic cleared - scar	
81	Keratitis	neg - culture		Antibiotic - R cleared	
82	Keratitis	neg - culture		Combo - cleared	
83	Keratitis	neg - culture		antibiotics cleared	
84	Keratitis	culture - staphylococcus		antibiotics cleared	
85	keratitis	culture - neg		antibiotics R cleared	
86	Corneal ulcer	fungal culture - don't remember which		Pimaricin corneal transplant	
87	Keratitis	culture - neg		antibiotics cleared	
88	Keratitis	culture - neg		antibiotics cleared	
89	Corneal ulcer	Pseudomonas - culture		antibiotics - scar - transplant	
90	keratitis	culture - neg		antibiotics cleared	
91	keratitis	culture - staphylococcus		R antibiotics cleared	
92	keratitis	neg - culture		R antibiotics cleared	
93	Corneal ulcer painful	Staph - culture		Antibiotics - transplant	
94	keratitis	neg - culture		R antibiotics cleared	
95	Corneal ulcer	culture - Pseudomonas		R antibiotics - scar - transplant (2 times) 1st transplant cleared	
96	keratitis	culture - neg		R antibiotics - cleared	

Clinic No.					
97	Kwashiorkor	Culture - neg	R. antibiotic		cleared
98	ulcer	Pseudomonas	R. antibiotic		Hospital
99	kwashiorkor	culture neg	R. antibiotic		cleared
100	Kwashiorkor	neg culture	R. antibiotic		cleared
101	Kwashiorkor	neg culture	R. antibiotic - 2 weeks - No drugs added Steroids - began to get better on 10 days - R.		
102	kwashiorkor	neg culture	antibiotic		cleared
103	Kwashiorkor	neg culture	antibiotic		cleared
104	kwashiorkor	neg culture	antibiotic		cleared
105	corneal ulcer	Culture - neg and culture neg but smear R. antibiotic -			Hospital
106	Kwashiorkor	Right Pneumonia	antibiotic		cleared
107	Kwashiorkor	neg culture	Penicillin		cleared
108	corneal ulcer	Pseudomonas	antibiotic		Hospital
110	kwashiorkor	diphtheria	antibiotic		cleared diphtheria neurological
111	kwashiorkor	neg culture	antibiotic		cleared
112	corneal ulcer	Culture - neg and culture gram but smear +		antibiotic -	staphylococcus
113	kwashiorkor	neg culture	Antibiotic		cleared
114	Corneal ulcer	Pseudomonas	antibiotic		Hospital
115	kwashiorkor	neg culture	antibiotic		Cleared
116	corneal ulcer	Culture - staphylococcus (anaerobic neg)	antibiotic		Hospital
117	Kwashiorkor	neg culture	antibiotic		cleared
118	Corneal ulcer	Staph	antibiotic		Hospital
119	kwashiorkor	neg culture	antibiotic		Cleared
120	kwashiorkor	neg culture	antibiotic		cleared
121	kwashiorkor	neg culture	antibiotic		cleared
122	kwashiorkor	diphtheria	antibiotic		cleared
123	kwashiorkor	neg culture	antibiotic		cleared
124	kwashiorkor	neg culture	antibiotic		cleared
125	Kwashiorkor	Positive culture - mixed (lower + smear what)	antibiotic		cleared
126	kwashiorkor	neg culture	antibiotic		cleared
127	kwashiorkor	neg culture	antibiotic		cleared

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	Adverse Reaction				
128	canal ulcer	- fungal culture	- [illegible]	6 pneumo	- transplant
129	Kirchner	culture - neg	Rx antibiotics		cleared
130	Kirchner	culture - neg	Rx antibiotics		cleared
131	Kirchner	diphtheroids	Rx antibiotics		cleared
132	Kirchner	neg culture	Rx antibiotics		cleared
133	Kirchner	neg culture	antibiotic Rx		cleared
134	canal ulcer	Staph	Rx antibiotics		transplant
135	canal ulcer	doesn't remember what other showed	Rx antibiotics	steroids	transplant
136	Kirchner	neg culture	Rx antibiotics		cleared
137	Kirchner	neg culture	Rx cleared on antibiotics		cleared
138	canal ulcer	culture neg	antibiotics		cleared
139	Kirchner	neg culture	antibiotics		cleared
140	Kirchner	culture neg	antibiotics		cleared
141	Kirchner	neg culture	antibiotics		cleared
142	Kirchner	neg culture	did not clear on 7 weeks of antibiotics - [illegible] cleared		cleared in 6 days
143	Kirchner	diphtheroids	antibiotics		cleared
144	Kirchner	neg culture	antibiotics		cleared
145	Kirchner	culture neg	antibiotics		cleared
146	Kirchner	neg culture	antibiotics		cleared
147	Kirchner	neg culture	antibiotics		cleared
148	canal ulcer	neg culture	no response to antibiotics		transplant
149	Kirchner	neg culture	antibiotics		cleared
150	Kirchner	neg culture	antibiotics		cleared
151	canal ulcer	culture - Staph	antibiotics - no response		transplant
152	canal ulcer	fungal culture	pneumo		transplant
153	canal ulcer	pseudomonas	antibiotics		transplant
154	Kirchner	neg culture	antibiotics		cleared
155	Kirchner	diphtheroids	antibiotics		cleared
156	Kirchner	pseudomonas - doesn't remember	antibiotics		cleared
157	Kirchner	neg culture	antibiotics		cleared
158	Kirchner	culture neg	antibiotics		cleared
159	Kirchner	neg culture	antibiotics		cleared
160	Kirchner	diphtheroids	doesn't respond to [illegible]		cleared in 6 days
161	Kirchner	neg culture	remembered to antibiotics only		cleared in week
			antibiotics		cleared

Admission	Random			
162	Kanchipo	cultures - slightly	R antibiotic	cleared
163	Kanchipo	cultures - neg	R antibiotic	cleared
164	Kanchipo (deleted)	cultures - neg ov	R antibiotic	cleared
165	Kanchipo	slightly	R antibiotic	cleared
166	Kanchipo	slightly	antibiotic	cleared
167	Kanchipo	cultures - neg	antibiotic	cleared
168	Kanchipo	neg - cultures	antibiotic	cleared
169	Kanchipo	neg cultures	antibiotic	cleared
170	Kanchipo	neg cultures	antibiotic	cleared
171	Kanchipo	neg cultured	antibiotic	not eligible for 5 days - added cleared chn in 6 days
172	Kanchipo	neg cultures	antibiotic	cleared
173	Kanchipo	slightly	antibiotic	cleared
174	Kanchipo	neg cultures	antibiotic	cleared
175	Kanchipo	cultures - neg	antibiotic	cleared
176	Kanchipo	cultures - neg	antibiotic	cleared
177	Kanchipo	cultures - neg	antibiotic	cleared
178	Kanchipo	cultures - neg	antibiotic	cleared
179	Kanchipo	neg cultures	Combo	cleared
180	Kanchipo	neg - cultures	antibiotic	cleared
181	Kanchipo	pos cultures - doxy	combo doxy	antibiotic cleared but c-xanthogran
182	Kanchipo	neg cultures	antibiotic	cleared
183	Kanchipo	cultures - neg	antibiotic	cleared
184	Kanchipo	all cultured often on antibiotics - neg	antibiotic	cleared on c-steroid good - got worse - D/c'd antibiotic & got better - cultured off antibiotic for 3 days
185	Kanchipo			
186	Kanchipo			
187	Kanchipo			
188	Kanchipo	neg cultures	antibiotic - cleared	
189	Kanchipo	neg cultures	antibiotic - cleared	

Chimney Pointers

190	[illegible]	[illegible] my mother	[illegible]	closed
191	[illegible]	mother - my	[illegible]	closed
192	[illegible]	my mother	[illegible]	closed
193	[illegible]	mother - my	[illegible]	closed
194	[illegible]	my mother	[illegible]	closed
195	[illegible]	my mother	[illegible]	closed
196	[illegible]	my mother	[illegible]	closed
197	[illegible]	grandmother	[illegible]	closed - purple rose
198	[illegible]	my mother	[illegible]	closed
199	[illegible]	my mother	[illegible]	closed
200	[illegible]	my mother	Cherokee	closed - purple [illegible]
201	[illegible]	fingers - especially	[illegible]	closed - purple rose
202	[illegible]	my mother	[illegible]	closed
203	[illegible]	mother - my	[illegible]	closed
204	[illegible]	my mother	[illegible]	closed - [illegible]
205	[illegible]	mother my	[illegible]	closed
206	[illegible]	my mother	[illegible]	closed
207	[illegible]	my mother	[illegible]	closed
208	[illegible]	Pandora	[illegible] -	[illegible]
209	[illegible]	my mother	[illegible]	closed
210	[illegible]	Chuyle	[illegible]	closed
211	[illegible]	[illegible]	[illegible]	[illegible] - [illegible]
212	[illegible]	my mother	[illegible]	closed
213	[illegible]	my mother	[illegible]	closed
214	[illegible]	my mother	[illegible]	closed
215	[illegible]	[illegible]	[illegible]	[illegible]
215	[illegible]	my mother	[illegible]	closed
216	[illegible]	my mother	[illegible]	closed
217	[illegible]	Pandora	[illegible]	[illegible]
218	[illegible]	my mother	[illegible]	closed

[illegible]

GARDNER (N)

MEMORANDUM OF MEETING

April 21, 1980

Between: Ms. Susan Leal, Subcommittee on Oversight and Investigations
Committee on Interstate and Foreign Commerce
House of Representatives

Dr. Kenneth Gardner, Subcommittee on Oversight and Investigations,
Committee on Interstate and Foreign Commerce
House of Representatives

and

Mary Bruch, Division of Anti-Infective Drugs, Bureau of Drugs

Dr. Arnauld F. Scafidi, Division of Anti-Infective Drugs,
Bureau of Drugs

Edward R. Melton, Office of Legislative Affairs

Ms. Leal requested this meeting to explore further a question which was posed in a February 25, 1980 letter to FDA from the Eckhardt committee:

> "What lead the FDA to conclude that salt tablets are not suitable for consumer use in caring for contact lenses, specifically, have there been documented adverse reactions?"

In responding to this question, Ms. Bruch first presented historical background concerning the use of salt tablets as well as the preserved saline solution with soft contact lenses. She said that the Bausch and Lomb soft contact lens was approved in 1971 and that review responsibility was transferred to the Division of Anti-Infective Drugs in January 1974. Ms. Bruch pointed out that the president of Soft Lenses, Inc., manufacturers of Hydrocurve lenses, would not have anything to do with the salt tablets for disinfection of their Hydrocurve lenses and he, therefore, pursued the research required to approve a preserved saline solution. This lens, with its preserved saline solution, was approved in April 1974. It was during the review and processing of this application by the Division of Anti-Infective Drugs that the inadequacies of the salt tablets for disinfection came to the attention of the Division staff.

Ms. Leal said that it was surprising to her that there were no printouts or other documented adverse reaction reports for the salt tablets. Dr. Scafidi explained the running account of adverse reaction reports that he has personally listed in a notebook totaling some 226 cases, all of which were related to the use of salt tablets. He said these cases involved keratitis, corneal ulcers, and other conditions. He also mentioned an article by Krachmer, which appeared in the Archives of Ophthalmology and gave histories of reactions to the use of salt tablets with soft contact lenses.

Both Dr. Scafidi and Ms. Bruch explained that the use of distilled water, which is purchased separately from the salt tablets, is a danger point for possible Pseudomonas contamination. The distilled water, which is sold in drug stores and supermarkets, is not produced under controlled conditions in many instances and, even if sterile at the time of purchase, it soon becomes contaminated. It was emphasized that where you have water, you are likely to have Pseudomonas contamination and that this organism will grow easily in distilled water.

Ms. Leal asked if there is any data on Pseudomonas in preserved saline solutions and both Ms. Bruch and Dr. Scafidi responded that the organism will not grow in these solutions.

Dr. Gardner asked how many cases we have of Pseudomonas infections and whether there is "hard data" on the incidence or prevalence of infections resulting from the use of salt tablets. Dr. Scafidi pointed out that it is practically impossible to get ophthalmologists to culture an infected eye condition. He said that this is primarily because of the fear on their part of malpractice suits. Ms. Bruch said that you cannot argue risk-benefit for a situation like this. She said admittedly the incidence of eye infections from salt tablets was rather small but, where they do occur, the consequences can be very serious. Dr. Scafidi said that the only data he has on clinical cases is what is regarded as "soft."

Dr. Gardner asked if the company were to do a study on salt tablets with a view to putting them back on the market, what would be required. Dr. Scafidi said that he had talked to Mr. Manelli of the Blairex Company concerning the requirements for a proper study of salt tablets, but that Mr. Manelli said he did not want to do any clinical study.

In response to a question about the preserved saline solution, Dr. Scafidi said he had only received one call on an adverse reaction associated with the use of this product.

To questions about the reports of adverse reactions from salt tablets from the Bausch and Lomb files, Dr. Scafidi and Ms. Bruch indicated that they had no knowledge of any such reports. It was again pointed out that adverse reaction reports are practically impossible to obtain from practicing ophthalmologists.

At the close of the meeting, it was agreed that we would send the committee a copy of the Krachmer study and a printout of reports from the Device Experience Network.

Edward R. Melton

SALT TABLET CHRONOLOGY

(1) March 18, 1971 - Soft lenses were approved for marketing - they were disinfected by using salt tablets and distilled water in a heating unit.

(2) May 24, 1976 - Action memorandum to Marion Finkel, Associate Director for New Drug Evaluation, from Merle Gibson, Director, Division of Anti-Infective Drug Products, concerning Federal Registry Statement on requirements for lens solutions. Memo states that by April 1974, "it was obvious that the salt tablet approach had difficulties associated with it..."

(3) June 3, 1976 - Memo from Finkel to Gibson recommends in response to May 24 memo that "salt tablets should be labeled as clearly secondary to use of preserved saline and to reserved for use only while traveling when preserved solution may be difficult to acquire." This issue to be addressed in the Federal Register.

(4) June 30, 1976 - Letter to Senator James L. Buckley from Robert C. Wetherall, Director of Office of Legislative Services. Letter states that soft contact lens system is "safe and effective for the labeling indications."

(5) July 19, 1976 - Medical Officer's Review of Annual Report (Dr. Scafidi) on the Bausch and Lomb contact lens. He reviewed the adverse reactions reported and stated "considering the number of lenses dispensed in this country (1.9 million) I feel the

incidence of adverse reactions is low but must be carefully monitored." He found that there were 85 adverse reaction reports, 3 were Pseudomonas.

(6) December 9, 1976 - Letter from Bausch and Lomb making commitment requested at a meeting with Bruch and Scafidi that once the preserved saline is approved B&L will phase-out salt tablets.

(7) December 27, 1976 - Letter from FDA, Merle Gibson to Bausch and Lomb - Discusses that there are many problems associated with salt tablets.

(8) January 25, 1977 - Results of study conducted by Bausch and Lomb. The results indicate that Burton-Parsons' Preflex (domestic) does not comply with U.S.P. specifications for a preserved solution. Specifically, the pseudomonas organisms do not reach the desired drop in concentration.

(9) January 28, 1977 - Letter to Merle Gibson from Bausch and Lomb. Restates commitment to market preserved solution but also states that solutions made with salt tablets are as safe and effective as preserved solutions.

(10) May 10, 1977 - Bruch memorandum intended to refute Bausch and Lomb accusations of failure of the Burton-Parsons solutions. (See B&L study, January 25, 1977). Bruch argues that the possibility of users not following directions is that "All

labeling warns against this." (p. 5). Bruch also describes the history of salt tablets as "unpreserved saline which has been a disaster". (p. 13)

11) May 12, 1977 - Letter from Merle Gibson to Burton-Parsons. Letter acknowledges supplement to their application made January 31, 1977 to use Burton-Parsons' preserved solutions with Bausch and Lomb lenses, and it is approved.

12) May 24, 1977 - Memo of meeting with FDA and Bausch and Lomb. Bausch and Lomb states their concern over use of their lens with Burton-Parsons' solutions. Dr. Scafidi emphasized the importance of providing proper labeling on lens cleansing solutions by reminding the members present that corneal transplants have resulted from the use of soft lenses with hard contact lens cleansing solutions.

13) July 20, 1977 - General letter to doctors from Bausch and Lomb. Recommending only the use of salt tablets.

14) August 10, 1977 - Bruch memo of meeting between representatives of FDA and Bausch and Lomb. B&L expressed continued concern regarding solutions to be used with their lenses and requested FDA to announce its policy in the Federal Register (p. 1.). Bruch said "she was afraid great effort would be expended (as B&L did to Burton and Parsons) ... to continue to make the applicants' (B&P) product appear risky and defective." (p.3)

Bruch's statement was made in response to B&L's request to see data before approval of a product is granted to be used with B&L's lens.

(15) August 31, 1977 - Medical Officer's review of Annual Report submitted by Bausch and Lomb - Covers period March 1976 to March 1977. Lists 95 adverse reactions, including 7 corneal ulcers but no indication of Pseudomonas.

(16) December 9, 1977 - Letter to Louis J. Spizziri from Mary Bruch, FDA. Letter was in response to Spizziri letter which supported the use of salt tablets for both clinical and monetary reasons. Mary Bruch rewrites in response: "FDA is constantly faced with anecdotal and testimonial evidence concerning both the effectiveness of a product and lack of toxicity or risk. However, we must deal with available objective facts and controlled studies rather than hearsay evidence."

(17) May 12, 1978 - FDA Chief Counsel Cooper letter (drafted by Scafidi) to FTC. At page 3: "Although FDA has been concerned for some time about the potential for serious patient injury from use of unpreserved saline solution prepared from salt tablets, it was not until early this year that an article was published demonstrating that our concerns are justified (J. Krachmer and J. Purcell, 'Bacterial Corneal Ulcers in Cosmetic Soft Contact Lens Wearers', Jan. 1978 Arch. Opthal. 57-61)."

(18) May 15, 1978 - Letter from Link, FDA, to Bausch and Lomb. (Draft prepared in Gibson's office). Letter sets forth "history" of salt-tablet difficulties. First point made is that instructions are not followed in using salt tablets - "the results may be disastrous. This potential has been recently realized and documented in [the Krachmer Study]". The letter concludes "FDA would appreciate communication from you to develop a schedule with you for the immediate withdrawal of the salt tablets from the marketplace."

(19) June 8, 1978 - Letter from Bausch and Lomb to David Link, FDA. B&L advises they have completed arrangements with another company for distribution of approved saline solution with B&L lens. B&L states they have no indication that many patients do not follow instructions for preparation of saline solution from salt tablets and requests data from FDA. B&L points out failure to follow instructions is not unique to use of salt tablets and refers to Krachmer study cited by FDA where failure to follow directions led to the difficulty of one of the persons described.

(20) October 27, 1978 - General letters to pharmacists and physicians from Bausch and Lomb announcing the arrival of preserved saline. Letter states that it is being done at request of FDA.

NDA 15-095

MAR 18 1971

AF 36-209

Bausch and Lomb
Soflens Division
Attention: Mr. William F. Coombs
635 St. Paul Street
Rochester, New York 14602

Gentlemen:

This acknowledges the receipt on March 16, 1971 of your communication dated March 16, 1971 enclosing printed labeling pursuant to your new drug application for "Soflens™ Contact Lens (polymacon)".

We also acknowledge your previous communication of March 9, 1971.

The application was filed on March 16, 1971.

We have completed the review of this application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

The enclosures summarize the conditions relating to the approval of this application.

Please submit two market packages of the drug when available.

Sincerely yours,

Henry E. Simmons, M.D., M.P.H.
Director
Bureau of Drugs

Enclosures:
Records and Reports Requirement (Reg. 130.13)
Conditions of Approval of NDA

cc: HDF-DO
NDA 15-095 orig., dup.
BD-100 (Dup-HO) BD-22 BD-242 BD-1
D/D-LJDeHaven-3/16/71
D/D init, LCHarris, RTorlath-3/16/71
Typed final-cem-3/16/71

NDA 16-895 January 7, 1971

Summary of Basis of Approval
(Manufacturing and Controls)

I. NDA 16-895

Bausch and Lomb, Inc.
Ophthalmic Division
635 St. Paul Street
Rochester, New York 14602

Non Proprietary Name: "Tolyuacon" (proposed USAN name)

Trade Name: Soflens™

Dosage Form: Prescription item

Category: Spherical ametropias and non-diseased eyes which have refractive astigmatism of 1:50 diopters or less and corneal astigmatism of 2:00 diopters or less.

II. Original Submission: October 20, 1969

Amendments: July 17, August 11, August 19, August 28, September 22, October 19, December 18, December 21, 1970 and January 4, 1971.

III. Controls

Components and Composition: 505(b)(2)(3) Satisfactory for composition of the solution.

Components of hydrogel
1. Poly (2-hydroxyethyl methacrylate) cross-linked with ethylene glycol dimethacrylate.
2. Distilled water.

Composition when in equilibrium with normal saline:
Cross-linked poly (2-hydroxyethyl methacrylate: 61.4% by weight
Water: 38.6% by weight

Microbiological challenge of the Aseptor Unit was conducted using the following organisms: Candida albicans, Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtitis and Herpes simplex.

No growth was evidenced in the culture tubes. The results indicate that the efficiency of the Soflens™ Aseptor units and submersion in boiling water are comparable.

Control Numbers: 5(a) — Satisfactory. A detailed explanation of the lot numbers is provided and illustrated by an example.

Stability: 5(p) — Satisfactory for the market package. Package stability tests include shelf life determination test, body temperature life test, accelerated life test, low temperature test, fitting set Aseptor test and freezing test.

Samples and Results: 505(b)(5) — Satisfactory. Samples submitted according to regulations, properly coded and accompanied by a protocol.

Labeling: Satisfactory. The following draft labeling has been submitted:

1. Shipping vial label.
2. Label placed on outside of styrofoam shipper.
3. Plastic sleeve.
4. Label on bottle containing sodium chloride tablets.
5. Label on one ounce plastic container for normal saline solution.
6. Package insert.
7. Instructions for wearers of Soflens™ Contact lenses.

MAY 2 4 1975

Associate Director
New Drug Evaluation (HFD-100)

Director, Division of Anti-Infective Drug Products (HFD-140)

Resolution of Policy Decision on Solutions for Lens Disinfection. Basis for a Federal Register Statement on Requirements for These Solutions. ACTION MEMORANDUM

INTRODUCTION:

Comments have been made previously by the Associate Director for New Drug Evaluation suggesting mechanisms for resolution of the problems associated with the marketing of multiple new lenses and new associated products for lens care. Some resolution is necessary to eliminate consumer risk and confusion. However, resolution may be difficult if the desires of the lens manufacturer and/or the solution manufacturer alone are considered for the following reasons:

1. Most lens manufacturers want specific solutions often bearing the same name as their lens.

2. Many solution manufacturers are willing to make these solutions.

3. However since it is possible that there will soon be at least a half-dozen lenses on the market the consumer will be faced with at least 3 different solutions for each lens. Often the consumer must return to the practitioner to obtain specific solutions and this may be an invitation for increased price to the consumer.

4. Some lens manufacturers have exclusive contracts with solution manufacturers.

If a solution manufacturer wishes to have one or more of their company's solutions sold as part of one or more systems, the solution can be packaged with the system or sold separately for use with a specific lens. The lens manufacturer may be allowed to submit data on the solution(s) with the NDA.

As an alternative, the solution manufacturer can establish a master file and let one or more lens manufacturers refer to it.

If the solution manufacturer wishes to take the initiative and wishes his product to be labeled for use with various lenses, then the manufacturer must submit an NDA or data to a Master File to show that his solution is appropriate for a specific lens.

Where solutions are referred to, heaters or sterilizers to be used to disinfect or sterilize may also be substituted.

Numerous clinical studies have been conducted using heaters as the means of disinfection. For each heater approved, microbiological studies to show effectiveness and chemical studies to determine accumulation and/or build-up of preservative materials in the lens as it is heated have been required.

Since the use of certain cleaners, disinfecting solutions or rinses in a disinfection regimen may cause alteration in the cul-de-sac flora and since the safety factors which can be calculated as a basis on which to judge the safety and effectiveness of the disinfection procedure should be use tested, at least one clinical study in which the solutions in question have been used in patients will be required.

All solutions should be clearly labeled as to which lenses and with which disinfection systems they can be used.

OBJECTIVE:

1. To simplify approval of disinfection systems for the manufacturer and to allow more than one procedure to be used with a given lens.

2. To assure that the patient can easily obtain the adjunctive solutions required for care of hydrophilic contact lenses.

FACTS:

A. SOLUTIONS

The development of hydrophilic polymers with their subsequent use as a contact lens material introduced to the contact

lens field a more comfortable lens without the spectacle blur common with hard lenses. The introduction of this new material also created problems which did not exist for hard lenses.

B. RATIONALE FOR DISINFECTION AND STORAGE

The hydrophilic lens must be kept wet at all times since if it becomes dry, it is useless as a lens. It would be naive and foolish to believe that a lens could be kept sterile during use by the patient. This however does not mean that the product should not be shipped from the manufacturer to the physician in a sterile condition.

It would be equally foolish to say that patients should place lenses in saline of the correct tonicity and suggest that these solutions not be preserved. In the care of hard lenses, cleaning storage solutions, in most cases, are preserved with combinations of antimicrobial chemicals. However, hard lenses are frequently stored dry and cleaned and moistened by the patient prior to insertion.

C. REGULATION OF LENSES AS DRUGS

During the very early development period with these new lens materials, when design and manufacturing procedures were studied and the very first clinical studies initiated, the use of preservatives in hydrating solutions and shipment of sterile lens was haphazard.

After several instances in which fungi and Pseudomonas were found in solutions and on lenses, the FDA felt that this situation, and the fact that there was limited clinical investigation of the lenses, required that these hydrophilic lenses be regulated as drugs.

The first two IND and NDA applications (after 1960) were from Bausch and Lomb and Griffin Laboratories.

Guidelines for investigation of these lenses were developed by an FDA Ad Hoc Advisory Committee. They developed no microbiological testing guidelines except that cul-de-sac culturing was recommended as part of the clinical examination protocol. The first microbiology testing guidelines were approved in October, 1973.

Regulation of tarsc and other ophthalmic drugs were transferred from Dental and Surgical Adjuncts (BFD-160) to Anti-Infective Drug Products (BFD-140) in January, 1974. Bausch and Lomb received approval of their NDA in 1970. This lens was approved using a salt tablet and distilled water to allow preparation of saline solution of correct tonicity so that the lenses could be removed from the eye, placed in the case in saline and heated at boiling temperature for approximately 15 minutes. This procedure appeared to be reasonable and effective. At this time, FDA and industry scientists had only recently become aware that some preservative chemical which would be required for a saline solution could accumulate in the polymer material of the lens and subsequently be released. If the chemical preservative concentrates in the lens, it could be toxic to the corneal epithelium. By the time a second lens was approved (April, 1974) it was obvious that the salt tablet approach had difficulties associated with it and that, furthermore, a preserved saline solution in a multiple-use container could be found which did not produce toxic effects from accumulated preservative chemicals in the lens. Soft lenses, Inc. obtained approval for such a system in 1974.

Three major problems have developed from use of the saline tablet.

1. The type of water, although distilled water is specified, cannot be controlled. De-ionized well water and tap water have been used with the result that deposits and coloration have been found in and on the lens.

2. The preparation of the saline solution is placed in the hands of the patient with the expected result that the tonicity of the saline used is highly variable.

3. The microbiological quality of distilled water is under local ordinance and is highly variable. Although any additional high load (of most client frequently be Pseudomonas or other gram negatives common in water) would be killed in the heating process, there could be high risk for individuals who for one reason or another neglect to heat their lenses. The growth of fungi in lenses (actually in the matrix of the lens) has been reported.

Patients may prepare saline and not use it or not use all of the supply and attempt to save it for another future use. Since there is no preservative, microorganisms may grow in the solution. This has occurred when patients have neglected to disinfect their lenses, often for a period of days or weeks. To date at least one infection has been implicated from fungi growing in a lens used therapeutically yet no infections have been reported in corrective lenses showing extensive fungal growth in the lens. However, the presence of fungi in the lens is a potential hazard to the wearer.

During this period Griffin Laboratories (now Warner-Lambert) applied for a license to market their lens (a polymer different from that marketed by Bausch and Lomb or Soft Lenses, Inc.) using hydrogen peroxide as the method of disinfection rather than heat. The Griffin lens was approved with heating as the means of disinfection for a single therapeutic indication.

The Warner-Lambert lens cannot be correctly heated for use in vision correction but can be heated occasionally for use in therapeutic indications.

Revised Guidelines and criteria for approval of a disinfection system have been developed and filed with the Hearing Clerk. Various chemical disinfection systems and heat at boiling and sterilization temperatures are being tested under these Guidelines.

Some chemical systems involve the use of more than one solution to achieve disinfection.

Pre-cleaners have been approved for use with hydrophilic contact lenses disinfected with heat and application for their use with chemical systems for disinfection has also been made. These pre-cleaners are usually a preserved detergent type cleaner. The major testing required is preservative testing.

A preserved saline solution has also been proposed for use as a rinse to remove the cleaner from the lens or to remove the chemical disinfectant solution from the lenses.

Several different types of chemical disinfectant soaking solutions are being tested. These solutions involve hydrogen peroxide, an iodophor, chlorhexidine, tallrexal, quaternary ammonium compounds ("quats") and combinations of chemical ingredients.

Since there is wide variation in the time period allowed or available to the patient for soaking lenses, a chemical soaking solution must achieve its effect within a four-hour period. This allows for a significant safety factor.

As the care of lenses by the patient has developed, the following products have been marketed:

1. Pre-cleaners -
   a. detergent, preserved.
   b. enzyme tablets - to be prepared by the patient.
2. Rinse solutions - preserved saline.
3. Boiling solutions - preserved saline solutions for use in the heat disinfection of the lens.
4. Chemical disinfectant soaking solutions.
5. Heaters which heat either to approximately boiling temperatures or at approximately 60 C.
6. Miniaturized autoclave units which heat at 121 C and are true sterilizers.

ALTERNATIVE COURSES OF ACTION:

A. Allow the current situation to continue. Each new lens manufacturer obtaining an NDA markets his lens with a solution for disinfection, rinsing, pre-cleaning or boiling or a boiler or autoclave for disinfection.

B. Permit manufacturers of disinfection or sterilization equipment or solution to clear a generic product with an NDA or set up a Master File for their products.

DISCUSSION

Each of these products will probably have a new commercial name although they will all be formulated by the same solution manufacturer. Continuation of this policy will confuse the consumer and the practitioner and it will prevent easy acquisition of lens care materials by the patient. Also the cost to the consumer will remain high when there is no choice of products.

The manufacturer of a boiler, autoclave or disinfection system should be able to market them for use with specific lenses. Some lenses, for example cannot be repeatedly boiled, others cannot be exposed to iodine, while some may accumulate preservative chemical such as quaternary compounds.

Any lens manufacturer must provide microbiological data for the overall disinfection or sterilization system with the lens being approved (USP-type, 20-liter test) and must demonstrate the degree of deposition, accumulation and release of preservative chemicals used in any disinfection or sterilization system.

The consumer wearing contact lenses of hydrophilic or new materials should be able to:

1. Have available at least one disinfection system which is effective with the wearer's lens.

2. Be able to purchase chemical solutions for heaters, sterilizers or for disinfection over-the-counter without having to return to the practitioner who fit the lens. As this situation now functions, consumers are often being overcharged for solutions.
   a. Indication should be made on the label of lenses which solutions or heating units have been shown to be safe and effective and indications should be made on solutions or heating units as to which lenses can be safely and effectively treated with them.

RECOMMENDATION:

There are two possible resolutions to the problem of multiplicity of techniques for disinfection developing concomitantly with a multiplicity of new of hydrophilic contact lenses.

1. A manufacturer of a disinfection or sterilization system of whatever type, either chemical solutions or physical, mechanical procedures must have a Master File which can be referenced by a lens manufacturer.

2. A manufacturer must have an approved NDA for the disinfection or sterilization system which a lens manufacturer can cross-reference.

Merle L. Gibson, M.D.

CONCURRENCES
Concur _____ Nonconcur _____ Date _____

PREPARED BY: BRUCH, HFD-140, 4/12/76, X34310

cc:
HFA-228
HFD-100
HFD-140
HFD-140/CSO
HFD-140/IXBruch:llb-4/28/76

(9)

JUN 3 1976

Director, Division of Anti-Infective
Drug Products (HFD-140)

Associate Director for New Drug Evaluation (HFD-100)

Lens Disinfection Solutions - Your Memorandum of May 24, 1976.

I concur that a manufacturer of a pre-cleaner, a solution or a chemical or physical disinfection process should have a Master File if he does not wish to market the product with his label and should have an approved NDA if he wishes to market with his label.

Your memorandum raised two other major issues which we should consider addressing in the F. R., in separate documents from the above but in the same issue:

1. To avoid confusion to consumers, and to avoid them having to hunt among pharmacies for the solution recommended by a lens manufacturer because it has his name on it, each lens manufacturer should list all brand names of solutions with which his lens has been found to be safe and effective.

2. The salt tablets should be labeled as clearly secondary to use of preserved saline solutions and to be reserved for use only while traveling when preserved saline solution may be difficult to acquire.

Marion J. Finkel, M.D.

cc:
HFD-100/Ms. Druch
HFA-228
HFD-140
MJFinkel:eks 6/2/76

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

(4)

Bausch & Lomb
Rochester New York
AF#36-809 FILE

Honorable James L. Buckley
United States Senate
Washington, D.C. 20510

JUN 30 1976

Dear Senator Buckley:

Your April 29 inquiry requesting a letter you received from Miss Evelyn J. Roberts, Tonawanda, New York, has been referred to us for further reply by Mrs. Virginia H. Knauer, Director, Office of Consumer Affairs.

A new drug application for the Bausch and Lomb soft contact lens was approved on March 23, 1971, after it had been reviewed and evaluated as adequate to show that this lens is safe and effective for the labeling indications.

We believe that Miss Roberts' difficulties may be isolated instances which can best handled through her optometrist and the Bausch and Lomb Company, as she has done.

Please let us know if we can be of any other assistance.

Sincerely yours,

Robert C. Wetherill, Jr., Director
Office of Legislative Services

Enclosure
Constituent's ltr

cc: Congressional Liaison Office

HFL-10 (2)
HFD-35
Office of Consumer Affairs (75479)

R/D:EKHelton
F/Tiarg:6/28/76

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE

United States Senate

Apr 1976

Respectfully referred to:

Congressional Liaison
Office of Consumer Affairs
Department of Health, Education,
and Welfare
330 Independance Avenue, S.W.
Washington, D.C. 20201

Because of the desire of this office to be responsive to all inquiries and communications, your consideration of the attached is requested. Your findings and views, in duplicate form, along with return of the enclosure, will be appreciated by

James L. Buckley
U.S.S.

Form #2

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
OFFICE OF THE SECRETARY
OFFICE OF CONSUMER AFFAIRS
WASHINGTON, D.C. 20201

May 25, 1976

Refer to: 75479

Honorable James L. Buckley
United States Senate
Washington, D. C. 20510

Dear Senator Buckley:

Thank you for bringing to my attention the letter from Miss Sandra J. Roberts regarding difficulties she encountered with her Bausch & Lomb soft contact lenses. Miss Roberts questions the perfection and the safety of such lenses.

As this is a matter under the jurisdiction of the Food and Drug Administration, I am forwarding this correspondence to the FDA for consideration and direct reply to you, with a copy to me. I hope this action will be helpful.

Sincerely,

Virginia H. Knauer
Director

Enclosure

cc: Food and Drug Administration
Rockville, Maryland 20852

Date: April 2, 1976

From: Sandra J. Roberts, 1 Valley Ct., Tonawanda, New York 14150

Regarding: Soft Contact Lenses (Bausch & Lomb--Soflens)

I received my soft contact lenses on August1, 1975. Their cost was $265.00 plus the eye exam. They were purchased from Dick O'Connor Optical, 4118 Union Rd., Cheektowaga, New York 14225.

I began having problems on January 19, 1976 when I noticed that my left contact had a slight tear in it. It was replaced at no cost because it was still covered under the six month warranty. We replaced the contact on January 26, 1976 however, the contact I received did not have sufficient power. I spoke to Mr. O'Connor about it and he said he would contact me when the new contact was in, I never received the phone call.

On February 26, 1976 the replacement lense broke while I was cleaning the contact with the soft-mate solution, it completely tore in half. I contacted Mr. O'Connor and the contact was replaced on February 27, 1976. At that time Mr. O'Connor gave me a different cleaning solution thinking this might be a possible answer to my problem. The new cleaning tablets were called Allergan (Stabilized Papain). This was also the left contact.

Again on March 15, 1976 I noticed that the left contact had a slit in it. I contacted Mr. O'Connor on March 16, 1976. I was unable to speak to him until March 17, 1976. After talking to him he suggested to me that the problem might be in the case in which I keep the contacts. The appointment before we had discussed the possibility of changing over to hard contacts and Mr. O'Connor suggested this again during our phone conversation. I told Mr. O'Connor that I had almost resolved to the fact of switching over. He then immediately set up and appointment for the following Wednesda

On our second appointment Mr. O'Connor suggested that we contact Bausch & Lomb. My father was finally able to contact their representative, Mr. Jack Shepphard, and was unable to get any satisfaction. We contact Mr. Sheppard on March 23, 1976 after the third tear. Mr. Sheppard had then told my father that he would be receiving a phone call from a representative of Bausch & LOmb in Rochester. As of March 26,1976 no calls or letter had been received to explain why this is happening or whether or not damage to the eye could occur wearing Soflens which could be defective.

I. E. Late Friday March 26, 1976 we did receive a call from Customer Relations of Bausch & Lomb. The woman was quite certain when asked the above questions that it could hardly be the lenses by indicating the Soflens were perfected and safe. It was her opinion that damaged lenses were caused by myself most likely in cleaning or placing them in the case. I question this by the fact that the both lenses were good for a period of five months then within a two month time lapse three left lenses eith tore, ripped, slit or broke in half. The Bausch & Lomb representative mentioned duri our phone call that a new carrying or storage case had been developed and they would send me one. (I might add it is a week later and I have not as yet received the case Please note: the cleaning process which is referred to is a device where the lenses are placed with the cleaning agent, distilled water and boiled, this is part of the Soflens kit. We feel Bausch & Lomb and the Optometrist are not being completely honest when they say these lenses are completely perfected and safe. On the plus side I had no trouble adjusting to them whereas, Mr. O'Connor did fit me with hard contacts lenses and I am now experiencing difficulty adjusting to them. At this time we still do not know anymore than we did when all these problems started. We would appreciate it if someone could find the answers and relay them to us. Thank you.

Sandra J. Roberts

Mr. & Mrs. J. Roberts

(5)

July 19, 1976

MEDICAL OFFICER'S REVIEW OF ANNUAL REPORT ON NDA 16-895

Sponsor: Bausch & Lomb
1400 N. Goodman St.
Rochester, New York 14602

I. Name of Product: A. Trade Name: Soflens Contact Lens

B. Generic Name: Polymacon Hydrophilic Contact Lens

II. Annual Progress Report R-89 for the Period from March 1975 to February 1976.

A. Clinical Data: There are final reports from 10 clinical studies included in this submission. There are additional 8 proposed clinical studies submitted. All the studies have been reviewed and revealed nothing new or unremarkable. The only one suggestion I would have for change in package insert if it was thought necessary is that persons wearing the lenses to sky dive should wear goggles when doing so.

B. Adverse Reactions: There are 85 adverse reactions reported. Just about every conceivable problem that has been involved with contact lenses has been reported. Since there are so many different types of lesions I do not feel analysis would be reasonable.

C. Labeling: The package inserts,labels for the varied types of lenses, patient instruction and clinician fitting manuals have all been reviewed and appear satisfactory.

D. Distribution: There were a total 2,303,016 lenses shipped.

III. Evaluation: Evaluation of this entire annual review reveals that further stress should be placed on proper care and disinfection of the lenses. It should be emphasized that careful scrutiny on the part of the clinician should be undertaken before patient is fitted with these lenses. The 85 adverse reactions revealed bacterial ulcers, mycotic ulcers, as well as viral ulcers. Allergy and scleritis along with intracorneal hemorrhages are also reported. Corneal molding with sequelae has also been reported. Numerous other problems such as errosion, staining, keratitis, abrasions, neovascularization, infiltrates, allergy, pannus, pterygian, corneal nebulae and palpebral lesion are also reported.

IV. Recommendation: Considering the number of lenses dispensed in this country (1,915,294) I feel the incidence of adverse reactions is low but must be carefully monitored.

A. F. Scafidi, M.D.
Division of Anti-Infective Drug Products

cc:
Orig NDA
HFD-108
HFD-140, HFD-140/CSO
HFD-140/AFScafidi:js 7/20/76

B. SUMMARY OF ADVERSE REACTIONS

March 1975-Feb. 1976

Name of Reaction	Report Returned	Total
Conjunctivitis	Recovered	8
Infections	Recovered	1
	No followup*	1
Erosions	Recovered	2
Injection	Recovered	5
Keratoconjunctivits	Recovered	3
Ulcer	Recovered	2
Ulcer (Mycotic)	Recovered	1
Ulcer (herpes Simplex)	Recovered	1
Ulcer (Bacterial)	Alive with Sequelae	1
	Recovered	1
Ulcer (Unknown)	Recovered	5
Staining	Recovered	5
Keratitis	Still under treatment	1
	Recovered	4
Abrasions	Recovered	12
Infiltrates	Still under Treatment	1
	No answer from physician	1
Neovascularization	Recovered	8
	Alive with Sequelae	2
	No reply	1
	Still under Treatment	1
Edema	Recovered	5
Intracorneal Hemorrhage	Recovered	1
Allergy	Still under Treatment	1
Scleritis	Recovered	1

*practitioner did not supply final report

Name of Infection	Reports Returned	Total
Palpebral Lesion	Recovered	1
Pannus	Recovered	1
Pterygium	Still under Treatment	1
Corneal Nebulae	Alive with Sequelae	1
Corneal Melding	Recovered	2
	Alive with Sequelae	1
Pseudomonas	Alive with Sequelae	3

VI. Distribution

A. The following is the summary of Production, Inventory and Lens Distribution.

Shipments	
Lenses Shipped to Practitioner	1,915,294
Lenses Shipped Export	387,722
TOTAL LENSES SHIPPED	2,303,016
Production and Inventory	
Initial Inventory	563,915
Lenses Produced (Net) in Period	2,621,008
Return from Customer	128,641
TOTAL LENSES AVAILABLE	3,313,564
Less Lenses Shipped	2,303,016
Less Lenses Used in Plant	247,691
FINAL INVENTORY	762,857
Lenses Distributed in New York State	172,376
Lenses Shipped in Interstate Commerce (Domestic)	1,742,918
TOTAL LENSES SHIPPED	1,915,294

(B)

BAUSCH & LOMB

PROPERLY SUBMITTED BY

ALAN A. KOPLAN

SUPPL NEW CORRES

December 9, 1976

M.L.Gibson, M.D.
Food and Drug Administration
Division of Anti-Infective Drug Products
5600 Fishers Lane
Rockville, MD 20852

Dear Dr. Gibson: RE: NDA 16-895

The attached labeling for Bausch & Lomb sterile preserved saline solution is submitted in conformity with our discussion on December 9, 1976 with Mrs. Mary Bruch and Dr. A. Scafidi.

We are also submitting at this time a letter from Mr. James P. Dodd, V.P. Bausch & Lomb, Inc., containing the commitment requested at the meeting.

Very truly yours,

William J Combs

AK/SN
Enc.

RECEIVED
DEC 9 1976
BUREAU OF DRUGS

BAUSCH & LOMB

EXECUTIVE OFFICES · ONE LINCOLN FIRST SQUARE · ROCHESTER, NEW YORK 14601 · (716) 338-6000

December 9, 1976

Marie L. Gibson, M.D.
Director, Division of Anti-Infective Drug Products
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

RE: NDA 16-095

Dear Dr. Gibson:

This letter will constitute a commitment by Bausch & Lomb that upon approval of the sterile preserved saline supplement to the above referenced NDA, a plan will be implemented to phase out distribution of SOFLENS® saline tablets. Once adequate supplies of the saline solution are available in retail outlets, we will discontinue all domestic sale of the tablets.

We further commit that upon approval of the supplement we will act expeditiously to initiate discontinuation of the saline solution.

Sincerely,

James P. Rodd
Vice President

JPD:jmr

69-139 O—80——6

(7)

ROD 2/15/79

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND

RECEIVED FDA
DEC 30 1976
W. F. COOMBS

DEC 2 7 1976

NDA 16-895 S-024

Bausch and Lomb
Attention: William F. Coombs
President and Technical Director
Soflens Division
1400 North Goodman Street
Rochester, New York 14602

Dear Mr. Coombs:

Your supplemental NDA 16-895 application (S-024) for the Aeseptron Heater was submitted on September 17, 1975 (submission date was September 16, 1975) after several meetings with FDA personnel to discuss the data, particularly microbiological studies, required for approval of this heater for lens disinfection. The basic premises in the submission were to eliminate the water required in the present Bausch and Lomb Soflens Heater and to change the time/temperature parameters of the heat disinfection cycle from approximately 100 C for 30 minutes to 80 C for 10 minutes. This heater provides a significant change in the heat disinfection parameters.

After submission of the supplement notification to FDA by Bausch and Lomb that this was an improvement over the currently marketed heater, a letter should have been sent to you notifying you that this supplement required review. Because of an oversight, this letter was not sent. However, Bausch and Lomb continued to meet with FDA to determine the appropriate data to be submitted. Were this a simple mechanical improvement, no such data would have been required.

At a meeting on November 11, 1976 the sponsor, Bausch and Lomb, through their attorney, expressed their belief that this supplement was only an improvement over a previously recalled heater. FDA

personnel stated at that time that they did not agree that this supplement only constituted an improvement but that it was a basic change in the disinfection regimen and should be reviewed and approved by FDA prior to marketing.

This letter is written confirmation of our view that this supplement should be reviewed prior to marketing of the unit. This view was re-affirmed at a second meeting and verbal commitment to express this in a letter to you was made with your firm on December 9, 1976.

Data from testing of a proposed preserved saline was unofficially submitted to FDA personnel on April 23, 1976. This contained extensive data which was later offically submitted as a supplement after considerable change in both manufacturer and formulation. An official supplement to NDA 16-895 (S-028) was submitted on September 16, 1976 and received by us on September 22, 1976.

These data and the subsequent official supplement concern the substitution of a preserved saline solution for the salt tablets currently marketed by your firm.

Salt tablets which are used by the patient to prepare a saline of the correct tonicity to hydrate the lens produce an unpreserved saline solution which can easily become contaminated. Many problems have been associated with the use of these tablets, so many, in fact, that no approval of other salt tablets has been made. Preserved saline solution is much more effective and convienient for the patient.

Microbiological data for the salt tablet with the new Aeseptron Heater and for preserved saline with two different proposed formulations and sources have been submitted over the past year. The disadvantages of the salt tablet are so great that this portion of the application will not be considered for approval with this heater.

In summary, both the supplement for the Aeseptron Heater (NDA 16-895 S-024) and the supplement for substitution of preserved saline for the salt tablets require review and approval prior to marketing.

No salt tablets have been approved for use with any other hydrophilic contact lens. The disadvantages in their use outweigh the benefits. Therefore, approval of the Aeseptron Heater for use with salt tablets will not be considered. The supplement for use of preserved saline with the Aeseptron Heater will be expeditiously reviewed.

Acknowledgment is made of your letter of December 9, 1976 signed by Mr. Dodd committing Bausch and Lomb to substitute preserved saline for salt tablets as soon as possible. It is noted that no date is specified in this letter by which these tablets will be unavailable. Without commitment, their marketing might continue indefinitely after approval of the preserved saline solution only for use with the Aeseptron Heater.

Sincerely yours,

Merle L. Gibson

Merle L. Gibson, M.D.
Director
Division of Anti-Infective
Drug Products
Bureau of Drugs

(8)

RESEARCH AND DEVELOPMENT REPORT FORM

BAUSCH & LOMB SOFLENS DIVISION

TO: M. Kaplan, Supervisor

FROM: L. Mandt, Biologist
D. DeWitt, Technical Assistant
E. Cohen, Technical Assistant

SUBJECT: Preservative Efficacy Test-Burton Parson's Domestic Preflex

REFERENCE:

DATE: January 25, 1977

TOTAL PAGES: 9

COPIES TO:

J.M. Szabocsik

SUMMARY

The results indicate that Burton-Parson's Preflex (domestic) does not comply with USPXIX interpretations of a preserved solution. Pseudomonas aeruginosa did not sustain a three log value drop in concentration for the duration of the testing period.

INITIAL

BAUSCH & LOMB OPTICAL CENTER · 1400 NORTH GOODMAN STREET · ROCHESTER, NEW YORK 14609

WILLIAM F. COOMBS
PRESIDENT AND TECHNICAL DIRECTOR
DEFENSE DIVISION
(716) 338-6000

January 28, 1977

Marie L. Gibson, M.D.
Division of Anti-Infective Drug Products
Food and Drug Administration
5600 Fisher's Lane
Rockville, MD 20852

Dear Doctor Gibson:

RE: NDA 16-093/S-024 (ASEPTRON™ Disinfecting Unit)
NDA 16-093/S-028 (SOFLENS™ Saline Solution)
SOFLENS® (polymacon) Contact Lens

The Administration letter of December 27, 1976, outlined a number of points concerning the above-referenced supplements. Rather than address each point specifically, we believe it might be more useful to consider them in three basic areas. These are: The Aseptron Disinfecting Unit (S-024); the SOFLENS Saline Solution (S-028); and the currently-approved SOFLENS® Salt Tablets.

1. Aseptron Disinfecting Unit (S-024)

This supplement was submitted on September 17, 1975. The submission followed the format set forth in 21 CFR 314.8(a) and, as called for by that section, was marked, "Special new-drug application supplement—Changes being effected." Receipt of the supplement was acknowledged by letter dated September 23, 1975.

Our letter of September 16, 1975, stated that the Aseptron Disinfecting Unit would provide increased assurance of safety, effectiveness and patient compliance. The principal improvement provided was the elimination of the need to add water to the unit itself. As you may recall, it was because of inadequate user care of the unit, associated with the need to use water in it, that led to the possibility of electrical shock which we reported to the FDA in early 1973. Elimination of this need, in our opinion, provided increased assurance of quality and increased the margin of safety. Additionally, the convenient compact size of the new unit provides greater certainty of regular use by the lens wearer, particularly when traveling. In the opinion of our consultants, the regulations permitted changes of this type to be made prior to approval and

it was on this basis that the supplement on the Aseptron Unit was originally submitted and the unit introduced to the market. Our legal counsel in the FDA matters subsequently advised us that having submitted the supplement as provided for by 314.8(d) and (e), we had an obligation to make the unit available.

During a meeting of November 11, 1976, we were informed that your division had completed its assessment of the unit, and the only elements remaining to be evaluated concerned its wiring and related aspects, and that a report on such evaluations by the Bureau of Medical Devices was anticipated within a week or two. No deficiency concerning any of the operational aspects of the unit has ever been communicated to us, and we know of none to date.

Regarding microbiological data, guidelines provided by the Administration provide that a time-temperature cycle of 80°C for ten minutes provides ample disinfecting efficacy. Both the Aseptor® - Patient Unit and the Aseptron™ Disinfecting Unit meet and exceed this specification, and both units achieve the required disinfecting results. Data relative to this aspect was, of course, provided to the Administration on September 16 and 29, 1975. Also, we should like to mention that the time-temperature parameter of 80°C for ten minutes for the Aseptron unit is a minimum specification with respect to time. Data previously supplied demonstrate that the average time above 80°C is 17 minutes.

2. SOFLENS™ Saline Solution (9-028)

The availability of a prepared saline solution for use in disinfecting the SOFLENS® (polymacon) Contact Lens would certainly be more convenient for many wearers of these lenses. But this is so irrespective of whether the heating unit is used is the Aseptor - Patient Unit or the Aseptron Disinfecting Unit, and considerations with respect to the approval of such a solution should be wholly independent of considerations involving the disinfecting units themselves. While it is our view that properly prepared solutions made with the salt tablets, which are currently approved for use in the disinfecting process for our lenses, are as safe and effective as a sterile preserved saline solution, we are nevertheless committed and anxious to make available to wearers of our lenses, as soon as possible, a solution known to us to have been prepared according to appropriate specifications and for which we can properly assume responsibility.

Our understanding is that there are no remaining questions regarding the SOFLENS Saline Solution. We are prepared to submit finished labeling immediately. You can be assured that once approval of the solution is received, we will initiate manufacturing and move this product to the market as quickly as possible.

3. SOFLENS® Salt Tablets

Via letter of December 9, 1976, our division president, James P. Dodd, notified the Administration that we would discontinue salt tablets once the preserved saline solution (SOFLENS Saline Solution) was approved for marketing and in distribution. At that time, we were unable to estimate the time required for the discontinuance. The Administration is hereby advised that the domestic distribution of our salt tablets will cease approximately six months from the date we receive approval to market the saline solution.

If we can provide any further information, we will be happy to do so.

Very truly yours,

WFCoombs/crp

(10)

Ed Metter
Legislative Affairs

May 10, 1977

MICROBIOLOGIST'S REVIEW OF NDA 16-895

Bausch and Lomb - Soflens (polymacon)

Subject:

Although this application is submitted to the Bausch and Lomb NDA, it deals with the use of Preflex, Flexol and Normol with the Soflens.

Introduction:

I met with Dr. Szobacsik and Mr. Anderson on March 18, 1977 (memo of meeting attached). At this time these representatives presented a brief summary of their accusations of failures of the Burton-Parson's system and their concern about use with their lens. This submission was subsequently made.

Confidentiality:

In the cover letter, the sponsor states that these data are confidential. However a copy of this material was sent to Burton Parson's when

the submission was made. I do not believe that it can any longer be considered confidential.

Seven short summaries are presented which seem disconnected. The major emphasis was that chlorhexidine is absorbed into the lens and produced a chromophore on analysis but this was not definitely established as to identity and that heating a lens in Flexol may distort and ruin the lens or that alternating heat and chemical disinfection for some time may cause deposits. There is a list of reasons therefore not to use the system:

A. Lens deposits were present after a one week soak in Flexsol. These deposits could be of clinical significance.

B. Lens deposits were present after one month of an alternating, chemical/thermal disinfecting regimen. Deposits did not develop to any significance after using GSH-1142-1959X for three months in an alternating, chemical/thermal disinfecting regimen[3]. It

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3. 1959X/Isontonic Saline Cycling Study, J. Mills, February 25, 1977.

is anticipated that patients will alternate between chemical and thermal disinfection of their lenses.

C. After one thermal disinfection in Flexsol, the lens was rendered nonfunctional. A lens thermally disinfected in GSH-1142-1959x was not adversely affected. It is anticipated that patients will alternate between chemical and thermal disinfection of their lenses. As a consequence, some patients may inadvertently disinfect their lenses thermally in the chemical disinfecting solution.

D. Chlorhexidine is absorbed (concentrated) by the lens and is eluted slowly. The presence of this preservative in the lens could be harmful to the physiology of the eye.

Comments on Above List:

A. Deposits on Soflens lenses soaked for 1 week in Flexol were found. The deposits were not identified and only 20% showed it. The degree was considered light but no scale was provided and evidently they were microscopic.

It should be recognized that the major reason for including the daily use of a precleaner is to prevent the daily build-up of deposits. This is a part of many and should be part of any care regimen.

It has been suggested repeatedly to Bausch and Lomb that they include a cleaning regimen in their system. To date no cleaner is recommended with the Bausch and Lomb system which is plagued with lens deposits and adherance with heating. Daily cleaning will prevent deposit formation. The saline solution in their regimen is used to rinse the lens and is not particularly effective. Bausch and Lomb has a long history of frequent lens replacement, so much so, that the whole lens field bears the stigma of frequent replacement of lenses, whether it is true of each lens or not, when improved care techniques are used.

The lenses were soaked continuously without cleaning or rinsing. This of course is not indicated in the labeling. Even if a wearer were to leave lenses in Flexol prior to wearing for a 7-day period, cleaning would precede it and rinsing would follow.

The deposits were not identified so that conclusions about them seem gratuitous.

This testing situation appears to be an artificial one designed for proving a particular point. The test was repeated with material obtained in U.S. after approval of the Burton-Parsons regimen here, since the first material was obtained in Canada.

B. The disinfection system mentioned by the writer is one which is not approved but is a quaternary compound which, if it concentrates in the lens, may be irritating. This procedure suggests that patients will alternate systems. All labeling warns against this. However, it may occasionally occur until clinicians and patients recognize the problems. The more likely situtation will occur where the patient is unable to purchase solutions or does not have access to the heater and will temporarily use heating in a pan or a chemical regimen until they go back to heat.

C. A series (8) of thermal disinfections in Flexol was performed with the Soflens lens and were measured, but not with the most sophisticated instruments. They found opaqueness and deposits microscopically. FDA and the manufacturer have been aware that heating HEMA lenses at the temperatures at which the wet heat disinfection units operate will cause irreversible

changes in the lens. As already stated, nowhere is it indicated that any lens should be heated in Flexol at these temperatures. It is surprising to me that the lenses could be heated with as little effect as reported by these investigators.

There is an inconsistency in the lens described as non-functional and several lenses described as no change.

It seems to be logical that two elements of Flexol were found on analysis, the chlorhexidine and the polymer components.

The concept that patients will alternate systems will probably only happen under the conditions mentioned. Bausch and Lomb patients might be more likely to have a heater available. However, if reports to FDA are correct, many patients will be eager to give up the outmoded task of preparing saline and using a disinfection unit, often with heat transmission from water.

D. The authors equate absorption with concentration of chlorhexidine in the lens.

FDA has been aware since they first approved preserved solutions that chlorhexidine and thimerosal are absorbed and bind to some degree to the lens material. In the beginning this information discouraged use of a preserved saline. We have much more information now.

We know more about the binding of chlorhexidine to the lens. It is a characteristic of this chemical to bind to binding sites on the surface of skin, paper, cloth and tooth enamel. The real question is, how much binds and how fast does it come out. In addition you need to know if the concentration increases with time. We have data for a number of lenses showing:

1. Chlorhexidine is bound to the lens.
2. The amount is small.
3. It elutes slowly
4. It does not concentrate.
5. Thimerosal also binds slightly and does not concentrate.

These studies were performed in vivo where equilibration with the tear film is measured and analyzed with radiolabeled chlorhexidine.

Bausch and Lomb has spent a long time promoting the use of an *in vitro* technique of applying a lens to an agar surface and measuring the zone of inhibition produced. In these studies the lens is similar to the antibiotic disc and subject to the same problems. The size of zone is determined by a multitude of test factors. The size of the molecule and its movement characteristics through agar are very important. This is a poor technique compared with the *in vivo* radiolabeled procedure.

Preservative Effectiveness Test

The techniques used in this study which reports that some solutions do not meet the FDA Preservative Test for lenses are disgraceful. The use of D-E (Dey-Engley) medium as a neutralizer when chlorhexidine is involved indicates that the experimentor is entirely unfamilar with testing chlorhexidine. This is not a good neutralizer for chlorhexidine. It is adequate for thimerosal. Tween is required in a chlorhexidine neutralizer.

Bacillus subtilis is inhibited from germination, as are some other spore formers in the presence of D-E neutralizer. It is unclear why this would be used as a test of the neutralizer.

The organic load of yeast cells was heated for 30 minutes when 5 - 10 is perfectly adequate and has been recommended by FDA.

Data have been presented from Burton-Parsons and Hazelton Labs and from repeated tests show preservative effectiveness for the three products under discussion.

Preservative Binding to the Lens

The binding of preservative to the lens was described in the report as strongly bound and tenacious. The description does not appear to be appropriate. The length of time or number of rinses required to remove all the traces of preservative from a lens may or may not indicate the degree of strength of the bond. It may also indicate the number and degree of saturation of binding sites.

The lenses were soaked for 18 hours prior to testing for zone of inhibition. Nowhere is it indicated to soak lenses for this period, although there is no problem in doing it. A normal 8-hour sleeping cycle would have been a more realistic test. Lenses are not soaked in either Preflex or Normol. As an objective test of a material, the time should reflect an exaggerated cycling.

68-5508 O—80——7

Biocidal Activity of Flexol

The same comments concerning technique apply to this test. The procedure is sort of a modified killing curve determination with attempts at extinction determination. The design is poor and the techniques have serious faults, particularly, the neutralizer used. The organism kill or survival contradict the data submitted to FDA on these products. It seems superfluous to execute a poor test like this when D-value work has been done and corroborated in FDA labs. Contradiction is seen when Aspergillus is killed and Staphylococcus survives. This is contradictory to the basic MIC data for chlorhexidine.

Cytotoxicity Testing

The lenses tested were soaked for 18 hours. The exaggeration would have been more reasonable if the lens had been cycled or exposed to the actual exaggerated use for the solution, i.e., soaking for Flexol, cleaning for Preflex or rinsing for Normol. The lenses were exposed to the solutions and then subsequently exposed to heating cycles.

best copy available

Cytotoxicity testing, was done by a rather routine technique. Positives were recorded as + or ± . There is no indication of other differences in degree. The positive effects were seen after the 18-hour soaks. A positive result was seen after the patient regimen with a specified minimum of exposure to Flexol of four hours (no exact time specified).

After 5 minutes in distilled water the cytotoxicity of Flexol was removed.

A letter from Dr. John Autian is included in the submission. Dr. Autian states that no plastic should have a leachable constituent. I would agree if such a constituent is a component of the polymer with potential toxicity. Statements of this kind are usually made with reference to implanted devices and subsequent interaction of leachable polymer components with body fluids. Dr. Autian appears to have little appreciation of the problems and intricacies of preserved versus unpreserved solutions for use in the eye. The intermittant nature of lens wear, the required disinfection regimen and the in vivo equilibration with tear fluid must be considered.

Hemolysis Testing

Protein Metabolism Test

Both of these tests were pursued to determine the effect of lenses soaked in the various solutions for the 18-hour time period on the hemolysis of rabbit red blood cells or on the inhibition of protein metabolism of mammalian cells.

Flexol testing showed that with this in vitro test, with several rinses or some time in distilled water before the hemolysis or protein inhibition test was performed, the effect was reversed. This effect was not demonstrated with Normol.

Comments on Cellular Inhibition Testing

These tests are entirely in vitro. We have a large amount of data showing a precise absorption of chlorhexidine and thimerosal. These preservatives equilibrate with the tear film and the amount stays rather constant. No attempt was made to do in vivo equilibration but all the work relied on artificial in vitro systems.

It has been known since a preserved saline solution was approved that some preservative binds to the lens.

In vivo testing and a rather extensive amount of use in patients has not revealed any problems in the use of this disinfection regimen, including use with the Bausch and Lomb lens. Since preservatives or active disinfecting chemicals are designed to be antimicrobial, and many of them affect the cell wall, it is not surprising that there is some effect in artifically structured *in vitro* tests.

The final tests are effectiveness and clinical results. The alternatives are unpreserved saline which has been a disaster or portion-packed pre-sterilized saline with no chemical disinfection. It should be noted that no other solutions, Boil N Soak, the proposed Bausch and Lomb Saline, nor the investigational Allergan disinfection solution were tested.

Some effect is bound to occur when a hydrophilic material such as HEMA is exposed to preservative chemicals. This must be weighed against effectiveness of the system and safety of alternative systems against any demonstrated risk.

In a study reported in this volume, the recommended Preflex, Flexol, Normol regimen was tested with several cycles with the Bausch and Lomb lens, and from their own statement, no adverse effect on the lens was noted.

Two recent references are attached to this review. One by Roth from the University of ULM emphasizes the critical importance of daily cleaning and disinfection on the wearability of the lens and on the growth on bacteria on the lens surface.

Nygren in a Swedish report (poor translantion) shows, in a rather carelessly contructed experiment, the effectiveness of lens disinfection. A solution being investigated for use with the Bausch and Lomb lens is discussed (Hydrocare, as it is called in Europe). Cytotoxicity is shown with this lens as well as wearer discomfort. This material was used comparatively in work submitted by Bausch and Lomb. It appears that it was included only where the argument against the use of Preflex, Flexol and Normol was better advanced. It was deleted where its own defects or adverse reactions might also be indicated.

Mary K. Bruch
Mary K. Bruch

cc:
Orig NDA
HFD-140
HFD-140/CSO
HFD-140/MKBruch:llb-6/14/77

MKB 6/16/77

(11)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

NDA 17-908/S-001

MAY 12 1977

Burton, Parsons and Company, Incorporated
Attention: John A Manfuso, Jr.
Central Industrial Park
Washington, D. C. 20027

RECEIVED
MAY 16 1977
Burton, Parsons & Co.

Gentlemen:

Reference is made to your supplemental new drug application of January 31, 1977, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Preflex and Boil n Soak Solutions.

We also acknowledge receipt of your additional communications dated February 15, 1977 and April 19, 1977.

The supplemental application provides for the use of Preflex and Boil n Soak Solutions with Soflens Contact Lens.

It is understood from the discussion by telephone on March 31, 1977 between your representative, Mr. John Manfuso, and Mr. William Kochert of this Administration, that the labels of Preflex and Boil n Soak will be changed at the time of the next printing to read, where appropriate "edetate disodium".

We have completed the review of this supplemental application and it is approved. Our letter of February 10, 1977, detailed the conditions relating to the approval of this application.

Sincerely yours,

Merle L. Gibson

Merle L. Gibson, M.D.
Director
Division of Anti-Infective
Drug Products
Bureau of Drugs

(12)

MEMORANDUM OF MEETING

FILE

AF 36-809

DATE: May 24, 1977

PARTICIPANTS: Representatives from Bausch & Lomb:

Mr. Burnside Anderson
Mr. Seymour Manello
Mr. Corwin Brumley
Mr. William Combs
Mr. Mark Shapairo (representing the law firm of Kleinfield and Kaplan, Washington, D.C.)

Representatives from Bureau of Drugs:

Mrs. Mary Bruch
Merle Gibson, M.D.
Arnauld Scafidi, M.D.

Representing the Bureau of Medical Devices:

Mr. David Link
James G. Dillon, Ph.D.

SUBJECT: Meeting with representatives from Bausch & Lomb concerning approval of new drug applications for accessory products.

The meeting was opened by Mr. Anderson stating that he and his colleagues were present to discuss their company's concern over the recent FDA approval of accessory products manufactured by other companies for use with Bausch & Lomb products. Bausch & Lomb had recently become aware of the approval of a competitor's disinfecting solution (Burton Parsons' Boil-n-Soak, Lens Rinse, Preflex) for use with Bausch & Lomb's FDA approved Softcon contact lens. The representative from Bausch & Lomb emphasized that his company was concerned both about the validity of their NDA file and that in the future many accessory products produced by other manufacturers may be approved for use with Bausch & Lomb's lenses.

At this point, Bausch & Lomb raised three questions: (1) what is the policy of the FDA concerning utilization of accessory systems with other manufacturers' lenses; (2) what is the policy of the FDA concerning referencing of NDA files; and (3) what quantity of testing is necessary by a manufacturer who wishes to distribute an accessory product for use with a competitor's lens?

505.5

At this point, Mr. Anderson posed the hypothetical question of whether Bausch & Lomb would be notified if the competitor changes the formulation of his accessory product which had been approved for use with the Bausch & Lomb lens. He continued by stating that this "new" policy of the FDA would have far reaching effects and could affect future testing systems, design changes, or formulation changes. Dr. Gibson replied that approval of the NDA for Bausch & Lomb Softcon lens had been granted before the Division of Anti-Infective Drug Products undertook examination of contact lenses and accessory systems. He continued by remarking that currently considerable confusion exists over the different systems available including saline. On June 3, 1976 his division had requested a policy decision regarding this matter.

At this point, Mrs. Mary Bruch commented that numerous complaints regarding saline had become available to the Division of Anti-Infective Drug Products indicating that some preservative must be included in the saline. She continued that it is now known, through radio-tracer studies, that preservative leakage is not a problem and further it was her Bureau's desire that the consumer have access to a wide variety of lens cleaning solutions. She emphasized that problems could arise if a consumer was unable to obtain the lens cleaner as recommended in the "system" marketed by one manufacturer. She stressed that the Bureau has always recommended that the various types of cleaning methods not be alternated as this may lead to undesirable interaction between the lens and the cleaning system being used.

Bausch & Lomb again reemphasized their concern about the future; interaction between disinfecting systems and lenses may become a problem. Bausch & Lomb questioned the laboratory capabilities of their competitors and pointed out that they have seen problems associated with interactions between their lens and currently used cleaning solutions. Bausch & Lomb remarked that when their company produces, for example, a new lens case, they examine all interactions that that case could be subjected to. Mr. Coombs pointed out that there may be 1,000 products to examine if all interactions were to be evaluated.

Bausch & Lomb continued by stating that they were disconcerted that they were not notified when other products had been approved for use with the Bausch & Lomb lens.

Mr. Link then asked if approval could be granted to a manufacturer who introduces a cleaning solution for use with one lens. The response to this question by Mary Bruch was that the manufacturer must test a representative sample of the marketed lenses or at least representative polymers currently used.

Dr. Scafidi emphasized the importance of providing proper labeling on lens cleaning solutions by reminding the members present that corneal transplants have resulted from the use of soft lenses with hard contact lens cleaning solutions.

A representative of Bausch & Lomb asked what would be required if Bausch & Lomb wished to use their saline cleaning solution with other lenses. Dr. Scafidi suggested that they submit an IND outlining a plan to examine 50 patients for three months if Bausch & Lomb was using an NDA approved lens by another manufacturer. Mr. Link asked if all solutions and lenses could be made interchangeable. Dr. Scafidi replied that he thought so, and that, in his opinion, it would probably remain feasible in the future.

Dr. Gibson expanded on a point made previously by Bausch & Lomb by stating that he thought all manufacturers involved in the approved product should be told that a lens and/or solution has been approved for use with the competitors' lens and/or solution.

Bausch & Lomb then asked how long it had been FDA's policy to require that saline preservatives be tested on all other lenses. Mary Bruch replied 18 months. In response to this, Bausch & Lomb asked when this policy had been required and not merely suggested. Mrs. Bruch responded that they had discussed this with Bausch & Lomb in the past and did not feel that this meeting was the place to rediscuss the issue.

The representatives from Bausch & Lomb again stressed their concern about interaction between their own products and products manufactured by other companies. Commenting on this remark, Mr. Link stated that the system approach now utilized does not work. A system consisting of one lens and one disinfecting solution manufactured by company A and another system manufactured by company B consisting of one lens and one solution have, despite warnings by the manufacturer, been used interchangeably by the public and that this has led to problems. Mr. Link then questioned whether any organization was working on standards development concerning lens accessory products. Mrs. Bruch replied that the first standard that should be issued would be one concerning saline preservatives.

In summarizing the meeting, Mr. Link stated that Bausch & Lomb now has been informed of the policy of the FDA. He granted that it is not an easy issue to resolve and desires that Bausch & Lomb inform the FDA if and when they become aware of the potential for interaction between their products and products manufactured by competitors. Bausch & Lomb responded by stating that standards indeed are an important issue in addition to correct labeling for their own products. They then requested information on how to make their products least harmful to the consumer. Mr. Link replied that the system approach appears to be of little benefit if the consumer does not read the label. A "matrix" approach would be much better where the manufacturer would concentrate on notifying the consumer, ophthalmologist, optometrist or optician what the incompatibilities are between their own product and products manufactured by competitors.

In conclusion, Bausch & Lomb requested that it would be of great benefit, in the future, if a letter could be prepared notifying when a competitor's product had been approved for use with their lenses.

The meeting adjourned at 2:15 p.m.

James G. Dillon, Ph.D.

cc: HFA-224
HFK-1 DMLink
HFK-470 JGDillon
HFK-470 JGD Chron
HFD-140 MBruch
HFD-140 MGibson
HFD-140 AScafidi

HFK-470/JGDillon/bmh/6/27/77

BAUSCH & LOMB

[illegible]

July 20, 1977

Dear Doctor:

Recent actions by the U. S. Food and Drug Administration and several soft contact lens accessory solution manufacturers have prompted many questions regarding the care of our SOFLENS® (polymacon) Contact Lens. The purpose of this letter is to clarify Bausch & Lomb's position.

Disinfection

The Bausch & Lomb patient care system has been proven to be safe, effective, economical, and convenient by well over a million users. Bausch & Lomb is currently testing various disinfecting solutions, both of its own formulation and those presently available. At present, we are not aware of any disinfecting solutions available in the United States that meet our requirements of safety and efficacy and prove to our satisfaction that there will be no long-term adverse effects to either patient or lenses. For this reason, we continue to recommend that only thermal disinfection be used.

Saline

Similarly, Bausch & Lomb has not received any evidence concerning preserved saline solutions currently available in the United States which would satisfy our long term concern for the lens wearer. For this reason, Bausch & Lomb recommends only the use of SOFLENS® Salt Tablets for preparing saline solution, used for lens rinsing, storing and thermal disinfection in the Aosept® or Aosept™ Disinfecting Units.

Cleaner

The SOFLENS® Enzymatic Contact Lens Cleaning Tablet is the only effective protein removing product Bausch & Lomb currently recommends for use with the SOFLENS Contact Lens. The use of these tablets on a regular basis is to free lenses of protein deposits and to prevent accumulation of those deposits. Bausch & Lomb has not seen evidence confirming the safety and efficacy of any other products currently offered for use in preventing protein buildup or its removal and therefore does not recommend any for use with our lenses.

(continued)

Warranties

Bausch & Lomb will, as always, stand behind the products it distributes for use with SOFLENS Contact Lenses. This includes the SOFLENS® Enzymatic Cleaner manufactured by Allergan Pharmaceuticals. However, as stated on our Sales Policy, claims for no-charge lenses under our Lens Performance Policy will not be honored unless the lens is cared for in accordance with instructions in the book "Instructions for Wearers of SOFLENS Contact Lenses." Lens problems arising from use of products not recommended or provided for in these instructions will have to be resolved by the practitioner or patient with the company that markets the product.

Bausch & Lomb has invested considerable time and money researching optimal lens care systems. The safety, efficacy, and economy of our current system has been demonstrated in over six years of clinical and wearer experience. When our research determines by adequate and thorough investigation that we are prepared to offer other systems which are compatible with the SOFLENS Contact Lens, we will notify you accordingly. In the meantime, if you have any questions regarding care systems for use with SOFLENS Contact Lenses, please telephone our toll-free consultation service. That number is (800) 828-9030, in New York State (800) 462-1720.

Thank you for your continued support of SOFLENS Contact Lenses.

Very truly yours,

Edwin H Brumley

See full prescribing information enclosed.

August 10, 1977 FILE

MEMORANDUM OF MEETING AF 36-809

Between:	Mr. William Coombs Mr. Bernard Anderson	Bausch and Lomb
	Mr. Alan Kaplan	Kleinfeld, Kaplan & Becker
	and	
	Marion Finkel, M.D.	FDA, NDE, HFD-100
	Merle Gibson, M.D. Arnauld Scafidi, M.D.	FDA, NDE, HFD-140
	Mike Pesco	FDA, General Counsel's Office
	Mary K. Bruch	FDA, NDE, HFD-140

This meeting was held at the request of Bausch and Lomb. They recalled that they had met previously with HFD-140 personnel on May 24 and with Mrs. Bruch again on July 26, 1977.

Mr. Kaplan reviewed the subject of these meetings saying that they had been informed about FDA labeling policy for new contact lenses at their May 24 meeting. They had concluded that Bausch and Lomb would not oppose this policy.

He also said that although this had been decided, they did believe that FDA should enunciate their policy in the Federal Register. Bausch and Lomb are concerned that changes in their own lens could

fect their lens and result in adverse effects with the lens or
t solution manufacturers might make changes which might have
verse effects on the lens. Mr. Kaplan felt that the situation
mplified in this meeting was very unusual and that a way of making
a available from an applicant for a lens to the applicant for a
lution and vice versa should be found. He hoped FDA would agree
d initiate such a mechanism.

. Pesco explained that FDA regulations prohibit opening files of an
A and that safety and effectiveness data are not available under
I. He said that the decision of safety and effectiveness of use
the solutions is decided by FDA on the basis of the data in
e application. Mr. Pesco added that he considered the problem
d solution a medical one and that Bausch and Lomb were transforming
into a legal one.

Bausch and Lomb does not agree or has contradictory data then
ere are procedural regulations already in effect that will allow
em to petition. He specifically informed Bausch and Lomb repre-
ntatives of the appropriate procedures. Mr. Pesco said that he did
t believe that such a change in policy should be generated within
A but would be much easier to implement if it were generated
tside, perhaps by an industry group.

Mr. Pesco added that from our point of view the interest of the consumer would not be served if, as in this case, Bausch and Lomb had seen Burton Parsons' data prior to approval of their disinfection system with the Bausch and Lomb lens. Mr. Pesco indicated that such a solution was only of interest and value to Bausch and Lomb. If such a procedure as suggested by Bausch and Lomb were to be implemented, the FOI regulations would have to be amended. Such a request would have to be reviewed as to whether it is altruistic or a power play. Mr. Pesco added the situation is not a unique one.

Mrs. Bruch commented that she was afraid great effort would be expended, as she had observed in this particular case, when experiments were apparently contrived to make the other applicants' product appear risky or defective. Such data had been discussed with and submitted to FDA by Bausch and Lomb concerning Preflex, Flexsol and Normol. Such maneuvers would likely confuse and delay approvals unnecessarily.

Dr. Finkel stated that she recognizes Bausch and Lomb's concern

about products to be used with their lens and hoped that firms making adjunctive products would cooperate with lens manufacturers and vice versa to make data available.

Mrs. Bruch and Dr. Scafidi stressed that this spirit of cooperation had been the rule and that Bausch and Lomb was the only firm making any issue of labeling of solutions to be used with their lens.

Mr. Coombs and Mr. Kaplan also discussed the caution label on Boil-N-Soak specifying that enzyme tablet should not be used with the Preflex/Boil-N-Soak lens care system. They claimed that they were unaware of any reason for this. Mrs. Bruch stated that she had discussed this at her July 26 meeting with the firms and with Mr. Coombs. She pointed out to Mr. Coombs that he had discussed Dr. Bosmann's work (University of Rochester, Department of Pharmacology) on residual enzyme on the lens. She added that Burton Parsons had presented data to FDA to support the labeling. However, she added, that this measure would likely be temporary until further data were submitted and the Allergan NDA was re-examined.

Dr. Finkel said that further discussion would be necessary internally and Mr. Pesco added that he felt initiation of such a change in regulation gested by FDA should be made by the industry.

Mary K. Bruch
Mary K. Bruch

cc:
Orig.
HFD-140
HFD-140/CSO
HFD-180
HFD-140/AFSc
HFD-100/MFin
HFD-MKBruch:h-77
GCF-1/MPesco
HFK-1/DLink
HFK-450/JDil
HFK-470/MTal

9/29/77

68-598 O—80——8

MEDICAL OFFICER'S REVIEW OF ANNUAL REPORT OF NDA 16-895

Sponsor: Bausch and Lomb, Inc.
Rochester, New York 14602

I. Name of Product:

A. Trade Name - Soflens Hydrophilic Contact Lens

B. Generic Name - Polymacon Hydrophilic Contact Lens

II. Annual Report R-10, March, 1976 to March, 1977.

A. Clinical Data:

There are a variety of clinical studies presented in relation to several of the spherical contact lenses the company currently has on the market. There are no major advances so far as the general overall knowledge of hydrophilic contact lenses are concerned. There is also a protocol for the evaluation of the two toric lens designs. These are currently undergoing in-house studies. When the FDA met with Bausch and Lomb on August 10, 1976, in Dr. Finkel's conference room, I reminded Mr. William Coombs that the Ophthalmic Device Advisory Committee said that before a toric contact lens could be put on the market a clinical study involving at least 50 patients for three months must be performed and submitted for evaluation. Mr. Coombs replied that he was not aware of this. At the time of our conversation Mr. Alan Kaplan, their General Counsel, was also present. They both asked where the Committee had made this recommendation. Mrs. Bruch replied that it was during a closed session on one of the Ophthalmic Device Committee meetings. I suggested to Mr. Coombs that he submit a IND for these studies to continue.

The next section of this annual review discussed the protocols involved in the evaluation of the sponsor's lens in the treatment of specified corneal diseases. This is an ongoing study as this product is already approved for many therapeutic indications. Several studies were presented relating the corneal thickness response to the wearing of the ultra thin Bausch and Lomb contact

lens. The sponsor's study states that the conclusion that can be drawn from this study is that there is less corneal edema than with standard thickness lenses. Some speculations was put forth that these possibly could be used as extended wear lenses. However, no data to support that statement was presented. Currently Bausch and Lomb is investigating the possibility of lathe cut rather than spin cast lenses. This is a very small in-house study. Apparently the first lenses produced were rejected by the Quality Assurance Control Group.

Several microbiology studies have been submitted. Many of these are on the Burton Parsons products, Preflex, Flexsol and Normol. They have been reviewed and a document dated May 10, 1977, entitled, "Microbiologist - Review of NDA 16-895. No further review is necessary. The sponsor has also submitted data evaluating the efficacy of the Hydrotherm II dry heat disinfection unit, the Burton Parsons lens care system. This medical officer does not feel any new data has been presented. Data on the evaluation of chemical uptake in the sponsor's lens, as well as detection of preservative in the cul-de-sacs, are presented.

B. Adverse Reactions:

There were 95 adverse reactions reported in this annual review. It is interesting to note that 6 of these reactions were post-use of the enzyme tablet. There were also 7 corneal ulcers reported in this group. However, there was only one reaction that has not been reported in the past with contact lenses. One clinician reported discoloration in the corneal endothelium and/or Descemet's membrane observable with the slit lamp. This discoloration consisted of light gray or gray blue appearance in the upper third of the cornea. There may also be slight increase vascularity in the upper third of the cornea associated with corneal deposits. This patient is still under treatment.

The package insert, patient instructions, labels for the lenses, the salt tablets, enzyme tablets and the new Acceptron are all included in this submission. They appear satisfactory.

C. Distribution:

There were 2,629,069 shipped during the past year.

III. Evaluation:

The sponsor has submitted data on several in-house clinical studies. No new data, so far as contact lenses in general, have been generated from these studies. The sponsor is also currently studying two toric lenses in in-house studies. There are no IND's for these at the present. There were 95 adverse reactions reported in this annual submission. However, there was only one that has not been reported in the past with contact lenses in general. In this one case there was some change in color of the upper third of the cornea associated with some possible vessel ingrowth and infiltrate. This patient is still under treatment. There were no new findings submitted in the microbiology data. It would appear from the labels submitted that Bausch and Lomb is now marketing their new dry disinfectant unit.

IV. Recommendation:

The recommendation has been made to Mr. William Coombs that the toric studies be continued under an active IND. The original Bausch and Lomb IND is still on active status.

Recommendation is also made that Mrs. Bruch's review of the microbiology data be attached to this annual report.

Arnauld F. Scafidi,M.D.
Division of Anti-Infective
Drug Products

cc:
Orig NDA
HFD-140
HFD-140/CSO
HFD-180
HFD-140/AFScafidi:mfh/8-31-77

DEC 9 - 1977

Louis J. Spizzirri, M.D., F.A.C.S., P.A.
350 Franklin Avenue
Wyckoff, New Jersey 07481

FILE

AF 36-809

Dear Dr. Spizzirri:

The approval of salt tablets as a mechanism for the preparation of normal saline was approved as a part of a heat disinfection system for the Bausch and Lomb Lens. This was approved very early before much information was available on uptake of preservatives by HEMA. There was fear on the initial discovery of preservative uptake that accumulation would occur. This does not happen although some preservative is bound to the lens material.

In the marketing and use experience, patients have used the wrong type of water resulting in tinting and deposits, have prepared the wrong tonicity solution with obvious results when the lens is worn, and worst of all, have allowed unpreserved saline solution to remain at room temperature and used it as a lens rinse and even applied it directly to the eye with the lens in place.

There is no doubt that some small portion of the population may be sensitized or became sensitive to mercury-containing compounds. However, if this occurs, the safe procedure is to have patients use sterile saline for injection which must be kept refrigerated. Unfortunately we are dealing with a very serious risk of corneal ulcer which occurs usually only after corneal abrasion. It is often difficult to persuade former hard lens wearers or fitters that the risks are significantly increased in water solutions in which lenses may be stored or to which a hydrophilic lens may be exposed.

FDA is constantly faced with anecdotal and testimonial evidence concerning both the effectiveness of a product and lack of toxicity or risk. However, we must deal with available objective facts and controlled studies rather than hearsay evidence.

The use of adequately preserved solutions in association with the eye is always preferred over a Russian roulette situation with unpreserved saline. There is certainly a need for an individual use saline dosage form for those individuals who cannot use preserved solutions.

Many reports of irritated and red eye, when investigated, have been the result of inadequate patient instruction, failure of the patient to rinse the lens and often, improper fitting.

When the risk/benefit is weighed, there is no place for the use of salt tablets or indeed any other tablet to be prepared by the patient/user.

Thank you for your interest in this subject.

Sincerely yours,

Mary K. Bruch

Mary K. Bruch
Microbiologist
Division of Anti-Infective
Drug Products
Bureau of Drugs

cc:
HFA-224
HFD-140
HFD-140/CSO
HFD-140/MKBruch:
11b-12/7/77

LOUIS J. SPIZZIRI, M.D., F.A.C.S., P.A.
350 FRANKLIN AVE.
WYCKOFF, NEW JERSEY 07481
AREA CODE 201
TELEPHONE 891-0200

October 28, 1977

The Director
Bureau of Drugs
The Food and Drug Administration
Washington, D. C.

Dear Sir:

I have recently read remarks by Mrs. Mary Bruch and Dr. Arnould Scafedi of your office. They state opposition to the use of salt tablets because patients make up the solution incorrectly. I have extensive experience with this product having fitted soft lenses since their introduction several years ago. To date, we have encountered no problems at all with salt tablets. On the other hand, I have encountered a very high percentage of reactions to the preserved salt solutions. In my opinion, the objections to salt tablets while theoretically plausible are found to be invalid in practice. The preserved solutions are considerably more expensive. The non-preserved sterile solutions are even more expensive. A non-preserved salt solution is essential for many patients who cannot use the preserved solutions.

Yours truly,

Louis J. Spizzirri, M. D.

dt
cc: The President
Bausch & Lomb Soflens Div.

Merle

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
OFFICE OF THE SECRETARY
ROCKVILLE, MD. 20852

May 12, 1978

OFFICE OF THE GENERAL COUNSEL

Michael E.K. Moras, Attorney
Division of Product Reliability
Bureau of Consumer Protection
Federal Trade Commission
Washington, D.C. 20580

Dear Mr. Moras:

This is in response to your letter of March 27, 1978, raising several questions concerning Bausch and Lomb's Soflens soft contact lens.

You asked for certain information to help you determine what action, if any, FTC should take regarding possible violations by Bausch and Lomb of the Warranty Act and the Federal Trade Commission Act. The possible violations concern actions by Bausch and Lomb to condition its warranty of soft contact lenses on the consumer's using Bausch and Lomb salt tablet solution to care for the lenses.

The information you requested follows:

1. Whether Bausch and Lomb is, or has been, legally required by FDA to instruct ophthalmalologists or other physicians and consumers that Bausch and Lomb salt tablets must be used in connection with proper maintenance of Bausch and Lomb soft contact lenses.

The labeling of the Bausch and Lomb Soflens contact lenses as approved for vision correction on March 18, 1971 (NDA 16-895) instructed consumers to use Soflens salt tablets to make saline solution and to use only the solution to wet, clean and store the Soflens contact lenses. Enclosed is a copy of this labeling, as well as revisions of the labeling that were approved on March 13, 1975, October 30, 1975, and January 13, 1976.

At the time Bausch and Lomb's original new drug application and these supplements were approved, the only tested and approved method for disinfecting contact lenses was heating them in the salt tablet solution.

After May 12, 1977, when preserved saline solutions became available for use with the Bausch and Lomb Soflens, Bausch and Lomb was no longer legally required to include labeling instructions to use only saline solution prepared from Bausch and Lomb salt tablets for lens wetting, cleaning, and storage.

2. The dates and names (including the names of manufacturers) of all other soft contact lens solutions approved by FDA to be used with Bausch and Lomb soft contact lenses.

On May 12, 1977, FDA approved NDA 17-908/S-001 (Preflex cleaner and Boil-n-Soak preserved saline solution) submitted by Burton, Parsons and Company. On the same date, FDA approved NDA 17-375/S-012 (Lensrins preserved saline solution), submitted by Warner-Lambert Company. The Preflex cleaner and the Boil-n-Soak and Lensrins saline solutions are the only preserved saline solutions which FDA has approved for use with the Bausch and Lomb Soflens. Enclosed are the approval letters sent to Burton, Parsons and Company and to Warner-Lambert Company.

On August 26, 1977, FDA approved Burton, Parsons' chemical disinfection regimen for cold disinfection (using Preflex and other products) of the Bausch and Lomb Soflens.

3. The dates and content of all notifications, whether oral or written, by FDA to Bausch and Lomb requesting the removal of the commitment to use Bausch and Lomb salt tablet solutions with Bausch and Lomb lenses and the names of Bausch and Lomb personnel notified.

FDA's principal concern is the safety problems presented by Bausch and Lomb salt tablets. To FDA, the question of securing changes in Bausch and Lomb's labeling to remove the instruction to use only saline solution prepared from Bausch and Lomb salt tablets is just one aspect of our general concern about the continued marketing of the salt tablets. FDA has communicated the agency's concerns about the continued marketing of these tablets to Bausch and Lomb on several occasions, including the following:

a) In a discussion with the firm on December 9, 1975, Mrs. Mary Bruch and Dr. A. Scafidi, FDA, requested a commitment from William F. Coombs, President and Technical Director, Bausch and Lomb that the firm would discontinue distribution of the salt tablets. On the same date, Mr. Coombs submitted to FDA a letter signed by James P. Dodd, Vice President, Bausch and Lomb, in which the firm provides a commitment that "[o]nce adequate supplies of [approved Bausch and Lomb preserved] saline solution are available in retail outlets, we will discontinue all domestic sale of the tablets."

b) On December 29, 1976, FDA sent a letter to Mr. Coombs in which the agency refused to consider approval of a new method using salt tablets because "[t]he disadvantages in their use outweigh the benefits." The letter also states that Mr. Dodd's December 9, 1976 commitment fails to specify any date by which the salt tablets will be unavailable.

c) On May 24, 1977, there was a meeting between Bausch and Lomb representatives and FDA representatives (memorandum enclosed) concerning approval of applications for contact lens accessories where FDA's concerns about the safety of the salt tablets were discussed.

In addition, Mrs. Lynch has explained FDA's concerns about the salt tablets at public meetings of the American Optometric Foundation (on September 12, 1976, October 23, 1976, September 12, 1977, and November 20, 1977), and of the Contact Lens Association of Ophthalmologists (in January 1977 and January 1978). All of these meetings were attended by representatives of Bausch and Lomb.

I am not enclosing copies of the letters dated December 9, 1976, and December 27, 1976 (described in paragraphs a) and b)), because they relate to a pending supplemental New Drug Application and because their disclosure may reveal confidential commercial information. These letters are not now available to the public under the Freedom of Information Act. Although we can provide you with copies of the letters under 21 CFR § 20.85 (copy enclosed), we will first need an agreement from your agency that FTC will not disclose the letters except with FDA's written permission. In your May 10, 1978 conversation with Linda Horton, you stated that you believed that only the Commission could enter into such an agreement.

4. Whether FDA may, on its own, remove said condition [i.e., the instruction to use Bausch and Lomb salt tablet solution with Bausch and Lomb lenses]; if so, why it has not done so; if not, what steps must be taken to remove it.

FDA has authority to require changes in the approved labeling of a product. If, for example, the device is unsafe or ineffective, or new information renders the approved labeling false or misleading, FDA may initiate a proceeding to withdraw approval of the premarket approval application under 21 U.S.C. 360e(e)(1). Such a proceeding is required to be supported by substantial evidence on the record taken as a whole (21 U.S.C. 360g(c)) and could be quite lengthy and complex.

Although FDA has been concerned for some time about the potential for serious patient injury from use of unpreserved saline solution prepared from salt tablets, it was not until early this year that an article was published demonstrating that our concerns are justified

(J. Krachmer and J. Purcell, "Bacterial Corneal Ulcers in Cosmetic Soft Contact Lens Wearers," Jan. 1978 Arch. Opthal. 57-61). A copy of this article is enclosed.

In the near future, FDA will formally communicate to Bausch and Lomb the agency's concerns about the continued marketing of the salt tablets. If the firm does not withdraw the salt tablets voluntarily, FDA will consider initiating an administrative proceeding to withdraw approval of the lenses or will take other appropriate action.

5. Any additional information that may be helpful to FTC's

Enclosed is a memorandum of a meeting on July 24, 1977, between Drs. Bruch and Bausch and Lomb representatives.

We hope this letter is helpful. If you need any additional information, please feel free to call me or Linda Horton.

Sincerely,

Richard M. Cooper
Chief Counsel
Food and Drug Administration

Enclosures

cc: M.L. Gibson, M.D. HFD-140
A.F. Scafidi, M.D. HFD-140
M. Bruch, HFD-140
R. Joyce, HFD-140
D.M. Link, HFK-1
J. Slaton, HFK-116
C. Schumer, HFC-10

MAY 15 1978

NDA 16-895

Bausch and Lomb
Soflens Division
Attention: Mr. William F. Coombs
635 St. Paul Street
Rochester, New York 14602

Dear Mr. Coombs:

This letter confirms the Agency's concerns about the continued marketing of salt tablets for heat disinfection of Bausch and Lomb's Soflens contact lenses. Representatives of the Division of Anti-Infective Drug Products have discussed these concerns in a number of recent meetings with you where they explained the Agency's desire that approved preserved saline solutions be available to patients for use with the Bausch and Lomb Soflens contact lenses, whether the solutions are marketed by you or by other manufacturers.

The Food and Drug Administration approved the use of patient-prepared saline solutions with the Bausch and Lomb Soflens at a point in the history of contact lens regulation when understanding of the uptake and binding of preservatives was new information. However, the second and every subsequent lens approved has been approved only with the use of sterile preserved saline in multi-use containers for heat disinfection.

We recognize that many patients have used the system of preparing saline from salt tablets, apparently without ill effects. However, the history of salt tablet use has also revealed a number of persistant difficulties:

1. Even though label instructions require daily preparation and disposal of saline by the patient, many patients do not follow these instructions. When a patient prepares the saline at less frequent intervals, the risk of microbial growth is magnified because the salt tablets contain no preservative. The longer the interval between preparation of fresh saline, the more likely it is to become contaminated. If a patient uses a contaminated solution to rinse the lenses or lubricate the lens in place, serious eye infection and possibly permanent injury to the eyes may result.

Frequently, the saline is mis-prepared resulting in either a hypotonic or hypertonic solution and/or lens and the patient experiences difficulty which occur when the tonicity is not correct. Please refer to the human clinical effects reported from the use of non-isotonic saline showing irreversible corneal thickening in animals and similar effects in humans. (Attached).

If the patient uses water other than the recommended distilled water, unacceptable deposits may result.

s. Much of the Division of Anti-Infective Drug Products has umerated these difficulties with salt tablets in several public rums at meetings of the American Optometric Foundation and for the ntact Lens Association of Ophthalmologists.

r desire to have preserved saline solutions available as an placement for salt tablets for Bausch and Lomb lenses has been scussed with you on a number of occasions. We also note that Mr. dd (in a letter dated December 9, 1976) committed Bausch and mb to removal of the salt tablets when preserved saline solution s available to the firm.

proved preserved saline solution manufacturers have assured us at they now have adequate production capacity to supply the needs current Bausch and Lomb lens wearers and newly fitted patients. ere has been no reason in the past and none has been put forth nce these products have been labeled for Bausch and Lomb lenses indicate any problems with the use of any marketed saline solutions th Bausch and Lomb lenses.

recent article (Arch. Ophthalmol, January, 1978) reviewing ases of corneal ulcers points to the misuse of saline and patients failure to make fresh saline each day as a critical fect in a regimen using salt tablets and, therefore, unpreserved lutions. If water solutions are used, allowed to stand and are preserved, the only reasonable conclusion by microbiologists ll be that gram negative organisms, particularly Pseudomonas, can expected to grow. Although patients can be expected to escape rious infection for some time just as in the cases reported, y are flirting with a dangerous situation, particularly if the rnea is accidently abraded. The patient may be even more likely use non-sterile saline if there is some discomfort after applying lens.

We are unpursueded by arguments of representatives of Bausch and Lomb that patients faced with increased cost of an approved preserved saline solution will resort to the use of unapproved materials. Certainly preserved, prepared saline is more convenient for the patient and the increased cost is minor when considered in relation to safety to the patient and the continuing risk for potential infection and injury if it is not used.

FDA would appreciate communication from you to develop a schedule with you for the immediate withdrawal of the salt tablets from the marketplace.

Sincerely yours,

/s/ David M. Link

David M. Link, Director
Bureau of Medical Devices

cc:
Orig. NDA
HFK-1
HFD-100
HFD-140
HFD-140/Joyce
HFD-140/Scafidi
HFD-140/Bruch/wh/5/5/78

BAUSCH & LOMB soflens
SOFLENS DIVISION · OPTICS CENTER · 1400 NORTH GOODMAN STREET · ROCHESTER, NEW YORK 14602
RUTHSIDE E. ANDERSON III
ATTORNEY AT LAW
DIRECTOR OF REGULATORY AFFAIRS
(716) 338-6514

RECEIVED
FDA/BMD
79 MAY 18 P
DOCUMENT CONTROL
CENTER

June 8, 1978

David N. Link (HFK-1)
Director
Bureau of Medical Devices
Food and Drug Administration
8757 Georgia Avenue
Silver Spring, MD 20910

SUBJECT: NDA 16-895 SOFLENS® (polymacon) Contact Lenses

Dear Mr. Link:

We acknowledge receipt on May 22, 1978 of the Administration's letter concerning the continued marketing of Bausch & Lomb Salt Tablets (hereinafter "Salt Tablets") for heat disinfection of Bausch & Lomb's SOFLENS® (polymacon) Contact Lenses.

As we previously advised the Administration, we have, for a long time, been planning to phase out distribution of Salt Tablets in favor of a preserved saline solution. However, we believe an orderly transition to the use of an approved preserved saline solution is necessary to assure that users of Salt Tablets will not resort to the use of unapproved materials to their detriment.

We have recently completed arrangements with another company for our distribution of an approved preserved saline solution under the Bausch & Lomb label. We are satisfied that this particular solution is compatible with our SOFLENS® Contact Lens. As a result, we will be able to provide continuity to the patient with a complete care system for the safe use of our lenses. Our labeling is currently undergoing revision to incorporate the preserved saline solution. When distribution of this product in retail outlets is complete, we will discontinue domestic marketing of Salt Tablets.

We have no indication other than your letter that many patients do not follow the instructions for preparation of the saline solution from Salt Tablets, and request that you make available to us the full facts upon which you rely in this respect. In any event, failure by some patients to adhere to instructions is not unique to any one product. Misuse is not a condition peculiar to Salt Tablets. As illustrated in the article from the Arch. Ophth. January 1978, to which you made reference, at least one case of infection may be attributed to the patient's failure to disinfect the lenses daily, rather than being caused by failure to follow instructions for the Salt Tablets. Thus, that incident would have most likely occurred under any circumstance. The second article referred to in the letter (British Journal of Ophthalmology; 62:1, 66-68 Jan 1978) is, in our opinion, merely speculative and does not establish that SOFLENS patients are preparing either hypertonic or hypotonic saline solutions from Salt Tablets.

BAUSCH & LOMB soflens®

We are certain that Salt Tablets are safe for use under the conditions of use upon the basis of which the application was approved. This is the statutory standard satisfied when NDA 16-895 was approved, and this standard continues to be satisfied. All patients wearing SOFLENS® (polymacon) Contact Lenses have been provided with easy to follow instructions for the daily preparation of saline solution from our Salt Tablets. These instructions provided for in our approved NDA 16-895 are found on the tablet bottle label and in the instruction for wearers booklet. Daily preparation and disposal of saline made from Salt Tablets is emphasized. Furthermore, the approved package insert for vision correction use includes adequate information to the practitioner concerning use of Salt Tablets. The practitioner is also advised not to dispense lenses to patients who would not or could not adhere to the recommended daily care of SOFLENS® contact lenses, including, of course, preparation of saline solution from Salt Tablets. When these directions are followed, there is no question but that Salt Tablets are safe for use under the conditions of use for which our NDA 16-895 was approved.

The current marketing of Salt Tablets by Bausch & Lomb has been based on their proven record of safety and efficacy when used as directed and not on any cost comparison to preserved saline solutions. Our instructions for daily care of our lenses have at no time prohibited the use of an approved preserved saline solution. The clinical experience generated by continued use of Salt Tablets by patients and their acceptance by practitioners is an endorsement of their safety and efficacy.

We will be pleased to meet with you to discuss a schedule for the orderly transition of present users of Salt Tablets to the Bausch & Lomb preserved saline solution once it becomes readily available.

The material and data in this communication is confidential and the protection afforded to confidential material and data by 18 U.S.C. 1905, 21 U.S.C. 331(j), 5 U.S.C. 552 and other applicable laws is hereby claimed.

Very truly yours,

REA:bs

BAUSCH & LOMB

Adopted

SOFLENS DIVISION - OPTICAL CENTER - 1400 NORTH GOODMAN STREET - ROCHESTER, NEW YORK 14602 - (716) 338-6000

HARRY B. MULKEY, JR.
VICE PRESIDENT
MARKETING SERVICES
SOFLENS DIVISION, USA
(716) 338-6207

October 27, 1978

Dear Doctor:

Effective November 1, 1978, SOFLENS® Salt Tablets will no longer be offered for sale. This is being done to assure patient care compliance and in response to a U.S. Food and Drug Administration request that Bausch & Lomb discontinue sales of the SOFLENS Salt Tablets. These tablets are used for preparation of normal saline solution for rinsing, storing, and disinfecting SOFLENS® (polymacon) Contact Lenses.

The Bausch & Lomb™ Sterile, Preserved Saline Solution, now available to your patients, eliminates the potential for patient non-compliance that existed with the salt tablet - distilled water regimen. Both Bausch & Lomb and the Food and Drug Administration feel a sterile, pre-mixed solution is desirable for your patients for a number of reasons.

The new solution is convenient for your patients because it's already pre-mixed; thus, there's no chance for mixing errors. It's available in an eight-ounce size for every day use and a four-ounce travel size. Instead of preparing fresh solution each day with a salt tablet and distilled water, it's estimated patients will have only to purchase one to two eight-ounce size bottles every month, depending on individual use.

The need for distilled water to prepare saline solution is eliminated. We have found the quality, composition, and availability of distilled water varies throughout the country. Now you can be assured your patients are using a uniform solution manufactured, controlled, and maintained under high pharmaceutical industry standards.

The preservative in the solution prevents potential problems resulting from lack of patient compliance with the daily mixing procedure.

Special mailing materials have been developed for you to alert patients about the discontinuance of salt tablets and the availability of Saline Solution. A sample is enclosed. You may order them free by returning the enclosed business reply card or calling Customer Service, toll free, at 800-828-9030 (800-462-1720 in New York).

Sincerely,

Harry B. Mulkey, Jr.

HBM:jc

Mr. GORE. I would like to thank you for the tremendous amount of work you have done, Dr. Gardner.

I have no questions.

Mr. Lent?

Mr. LENT. No questions.

Mr. GORE. With the thanks of the subcommittee you are excused at this point.

Dr. GARDNER. Thank you.

Mr. GORE. We would like to call now our first panel of witnesses: Mrs. Mary Bruch, microbiologist, Division of Anti-Infective Drug Products, and Dr. Arnauld Scafidi, ophthalmologist and medical officer, Division of Anti-Infective Drug Products, Food and Drug Administration.

Mrs. Bruch and Dr. Scafidi, if you would stand and raise your right hands.

Do you swear to tell the truth, the whole truth, and nothing but the truth, so help you God?

Mrs. BRUCH. I do.

Dr. SCAFIDI. I do.

Mr. GORE. Each of you is accompanied by counsel. Let me advise you that under the Rules of the House of Representatives the role of counsel in these proceedings is confined to advice on constitutional rights. I would be pleased to recognize you for an opening statement if you have one, beginning with you, Mrs. Bruch.

TESTIMONY OF MARY BRUCH, MICROBIOLOGIST, DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS, FOOD AND DRUG ADMINISTRATION, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH AND HUMAN SERVICES, ACCOMPANIED BY DANIEL G. GROVE, COUNSEL; AND DR. ARNAULD SCAFIDI, OPHTHALMOLOGIST AND MEDICAL OFFICER, FDA, ACCOMPANIED BY BROUGHTON M. EARNEST, COUNSEL

Mrs. BRUCH. I have no statement.

Mr. GORE. Dr. Scafidi?

Dr. SCAFIDI. I have no statement.

Mr. GORE. Dr. Scafidi, Dr. Gardner of the subcommittee staff just described to us a report that you made to the registry of drug-induced ocular side effects. They have listed 201 problems associated with salt tablets and 196 of those problems were given to them by you in one fell swoop.

When subcommittee staff asked you about this matter and asked you about allegations that some of these reports were manipulated—some of the data were manipulated—you showed the staff a notebook [see p. 42] and stated that you used the notebook to record a running account of adverse reaction reports furnished to you by clinicians whose patients have experienced corneal infections from using salt tablets in the care of their soft contact lenses. Is that correct?

Dr. SCAFIDI. I showed them a notebook that I had put together which I carry with me when I go to meetings, such as this one.

Mr. GORE. You stated that of the reaction reports listed numerically in your notebook, approximately 60 percent were furnished to

you by doctors at various professional meetings that you attended. Is that correct?

Dr. SCAFIDI. That is correct.

Mr. GORE. And that the remainder were reported to you by telephone, both at home and at FDA. Is that right?

Dr. SCAFIDI. That is correct.

Mr. GORE. You told the staff that you maintained this notebook for quite some time. Is that also correct?

Dr. SCAFIDI. I maintained these small notebooks when I came to FDA. When this question came up last August I simply combined it into one larger notebook. That is what I showed the staff.

Mr. GORE. Of course, you told the staff something different in their interviews with you. You told them that you had compiled the large notebook for a period of 4 years and that you had taken that notebook with you to these professional meetings and took it home with you at night. Did you not tell the staff that?

Dr. SCAFIDI. If I did, I do not remember, or they must have misunderstood me.

Mr. GORE. I can bring the four staff members who were present and put them all under oath. Their recollections are all the same, and all four of them heard you say that. I believe at one point an employee of the FDA liaison staff was also present. Are all five of these people having memory problems?

Dr. SCAFIDI. I don't know. If that is what I said, I said that, but it certainly was not what I meant to say. I don't carry a large notebook. I carry small ones with me.

Mr. GORE. Mr. Edward Melton with the Office of Legislative Affairs for the Food and Drug Administration sat in on one of the interviews between you and our subcommittee staff. His memory is that you kept a running account in this notebook.

You are now saying something different. You are saying that you took small notebooks with you.

Dr. SCAFIDI. That is right.

Mr. GORE. And then transcribed them into the larger notebook.

Dr. SCAFIDI. That is exactly right.

Mr. GORE. Which accounts for the fact that the notebook which you had earlier told us you took with you all the time was no worse for wear.

Dr. SCAFIDI. No, it was not worse for wear. It was a relatively new notebook.

Mr. GORE. When did you transcribe the smaller notebook into the larger notebook?

Dr. SCAFIDI. August or September of 1979, some time around then.

Mr. GORE. On how many occasions did you do it?

Dr. SCAFIDI. I do not remember.

Mr. GORE. The data you had compiled, the data given to you by doctors at these meetings and in telephone calls to your home and at your office, this was over a 4-year period. Is that correct?

Dr. SCAFIDI. Yes, sir.

Mr. GORE. In August of 1979, you then took the smaller notebook and compiled them into the larger notebook?

Dr. SCAFIDI. Yes, sir.

Mr. GORE. If it has been going on for 4 years, then at that point in August of 1979 you took 3 years' worth of earlier reports and put them into the larger notebook. Is that right?

Dr. SCAFIDI. Yes, sir.

Mr. GORE. Did you do that all at one time?

Dr. SCAFIDI. I don't believe so. I just don't remember.

Mr. GORE. Did you do it a little bit at a time? Did you do it in one sitting?

Dr. SCAFIDI. I don't remember.

Mr. GORE. There are over 200 of these entries in the notebook. That was bound to have taken a long time. It seems to me as though it is something you would remember.

Dr. SCAFIDI. I never gave it much thought at the time. I just did things as they came.

Mr. GORE. I want to come back to this, but let me ask a couple other questions first about the nature of the information. This is the information that is now being used to justify a decision that has cost American consumers $200 million annually.

Why is there no doctor's name associated with each of these entries?

Dr. SCAFIDI. First of all, the Privacy Act does not allow me to release doctors' names. I was told of that when I first came to FDA.

When I am at a meeting, when I talk to a man, I write down in rough notes—I wrote down in rough notes—what he told me, and kept it in my notebook. When I compiled the notebook I was aware of the fact that I cannot give doctors' names.

The notebook was simply something that I was trying to determine myself whether there was a salt tablet problem to the scope which everybody thought.

Mr. GORE. Are you familiar with this report—would the staff please give him a copy? [See p. 35.]

Dr. SCAFIDI. I am familiar with it.

Mr. GORE. You are the project officer on this study?

Dr. SCAFIDI. I most certainly am.

Mr. GORE. This report form is the one which is supposed to be used to file information with this registry, the same registry to which you reported 196 cases of problems with salt tablets.

[The document referred to follows:]

DRUG EXPERIENCE REPORT *(In Confidence)*

This report is authorized by law (21 CFR 310.305). While you are not required to respond your cooperation is needed to make the results of this survey comprehensive, accurate and timely.

Form Approved; OMB No. 57-R0071
Use of this form is prohibited after June 1980

PATIENT INITIALS (Optional) | AGE | SEX ☐ ☐ | DATE OF REACTION ONSET

SUSPECTED REACTION(S) (We have particular interest in serious, rare and unusual reactions.)

Sample 2

SUSPECTED DRUG(S); TRADE/GENERIC NAME (Manufacturer's name, if possible)

DISORDER OR REASON FOR USE OF DRUG(S) (Optional) | ROUTE | TOTAL DAILY DOSE | DATES OF ADMINISTRATION

OTHER DRUGS TAKEN CONCOMITANTLY

COMMENTS (Optional)

PHYSICIAN'S NAME, ADDRESS, AND ZIP CODE

FORM FDA 1639a (7/79) PREVIOUS EDITION MAY BE USED.

F. T. Fraunfelder, M.D.
National Registry of Possible Drug
Induced Ocular Side Effects
University of Oregon, Health Sciences Center
Department of Ophthalmology
Portland, Oregon [redacted] 97201

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F. T. Fraunfelder, M.D.
National Registry of Possible Drug
Induced Ocular Side Effects
University of Oregon, Health Sciences Center
Department of Ophthalmology
Portland, Oregon [redacted] 97201

Mr. GORE. Why did you not use one of these forms? You are the project officer on this project.

Dr. SCAFIDI. Because it is a lot easier for me to dictate something I hear and send it to them that way.

Mr. GORE. This form calls for the name of the doctor, does it not?

Dr. SCAFIDI. Yes, sir, and that form is strictly voluntary. You do not have to put your name on that form if you do not want to.

Mr. GORE. But you are the project officer.

Dr. SCAFIDI. So what? I still don't have to put my name on the form. It is a voluntary form.

Mr. GORE. Is it not true that most adverse reaction reports in FDA have the doctor's name on it?

Dr. SCAFIDI. When I see them, most of the time, yes, but that is in confidentiality. I cannot release that name. That is an entirely different form when it comes in in the IND or NDA.

Mr. GORE. Your notebook was confidential, was it not?

Dr. SCAFIDI. The notebook was just mine, something I was collecting trying to determine for myself if indeed there was a problem and the extent of it. It was never meant to be anything more than that.

Mr. GORE. So you do not have any doctors' names associated with each of these reports. You say in 40 percent of the cases people called you at home. Did they give you their names over the telephone?

Dr. SCAFIDI. Sure they gave me their names.

Mr. GORE. On all occasions?

Dr. SCAFIDI. Well, I am not sure if they gave them to me on all occasions. People speak so fast sometimes I don't catch their names.

Mr. GORE. You told our subcommittee staff in some cases they muffled their voices.

Dr. SCAFIDI. That is right.

Mr. GORE. Why?

Dr. SCAFIDI. Because doctors are afraid of malpractice. Besides, there is no approved use for salt tablets on the market now as far as soft contact lenses go. They don't want anybody to know they have had a problem like this.

Mr. GORE. So a lot of these reports were called in to you after you had gotten the salt tablets taken off the market, and they were afraid that they would get into trouble because their patients were still using salt tablets?

Dr. SCAFIDI. Yes, sir.

Mr. GORE. That is why they muffled their voices?

Dr. SCAFIDI. One of the reasons, yes, sir.

Mr. GORE. Did it appear they put a handkerchief over the telephone, their tie, or could you tell?

Dr. SCAFIDI. I am not very good at muffling my voice. I have never tried it so I wouldn't know what method people use to muffle their voices.

Mr. GORE. All right. Let's go back to the notebook. You took 3 years' worth of reports from these small notebooks. Could you let me see one of those small notebooks again?

Dr. SCAFIDI. Yes.

Mr. GORE. Where are the small notebooks you carried with you from which you transcribed the data?

Dr. SCAFIDI. Where?

Mr. GORE. Yes.

Dr. SCAFIDI. In the trash can.

Mr. GORE. You threw them away?

Dr. SCAFIDI. Once I accumulated all this data I threw them away. They were beginning to drive me out of the office.

Mr. GORE. We would like to see this notebook. Is this a relatively new one?

Dr. SCAFIDI. Yes.

Mr. GORE. If you could hand that to subcommittee staff.

Dr. SCAFIDI. Are you going to give it back to me?

Mr. GORE. Yes, we will give it back to you.

This is one that you currently are using?

Dr. SCAFIDI. Yes, sir.

Mr. GORE. Is that right?

Dr. SCAFIDI. Yes.

Mr. GORE. The information required in the social report includes sex and age in addition to physician's name. None of that data was reported to the registry either. Is that right?

Dr. SCAFIDI. No, because I didn't get it.

Mr. GORE. Why didn't you get it?

Dr. SCAFIDI. Because I was just trying to find out if indeed there was a problem worthwhile going after clinical study.

Mr. GORE. How many of these notebooks did you use and then transcribe into the larger notebook?

Dr. SCAFIDI. I have no idea.

Mr. GORE. At any point in August 1979 you sat down and transcribed 3 years' worth of those notebooks into the larger notebook. Is that correct?

Dr. SCAFIDI. I started in either August or September 1979.

Mr. GORE. Let's take a look at the notebook that you transcribed this data into. I would like to ask the staff to give the witness the original notebook.

[Testimony resumes on p. 141.]

[Staff observations and Dr. Scafidi's notebook follow:]

Dr. Scafidi's Notebook

It is apparent that there are distinctive differences in the colors of ink and/or the pens used to record the 228 entries in this notebook. At least 5 pens and 4 colors of ink (dark black, light black, red, and blue) were used. It appears that either the color of ink and/or the pen was changed 20 times in recording these entries.

	Entries	Number	Description of color of ink and/or pen used
(1)	1 - 5	5	dark black
(2)	6 - 9	4	light black
(3)	10 - 12	3	red
(4)	13 - 20	8	light black (dull point)
(5)	21 - 25	5	light black (sharp point)
(6)	26 - 31	6	light black (dull point)
*(7)	32 - 36	4	light black (sharp point)
(8)	37 - 41	5	light black (dull point)
*(9)	42 - 66	25	light black (sharp point)
(10)	67 - 70	4	blue
(11)	71 - 77	7	dark black
(12)	78 - 85	8	light black (sharp point)
(13)	86 - 96	11	blue
*(14)	97 - 153	57	light black (sharp point)
(15)	154 - 161	8	blue
(16)	162 - 174	13	light black (sharp point)
(17)	175 - 189	15	dark black
*(18)	190 - 222	34	light black (sharp point)
(19)	223 - 226	4	dark black
(20)	227 - 228	2	light black (sharp point)
		228	

* Omitted numbers 35 and 108;
duplicated numbers 43, 121 & 215.

7530-00-286-6952
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Advance Reader

1. corneal ulcer – cultured ++ Rare org – R antibiotics – cleared pinpoint scar
2. Keratitis – cultured – P.aeruginosa – R antibiotics – cleared no scar
3. Keratitis – cultured – no org – R antibiotics – cleared
4. corneal ulcer – cultured pseudomonas – R antibiotics + transplant
5. Keratitis – cultured – diphtheroids – R antibiotics – cleared
6. Keratitis – cultured – no org – R antibiotics – cleared
7. Corneal ulcer – cultured – Staph – cleared + antibiotics
8. Keratitis – cultured – no org – Candida – cleared Amb – cleared
9. Corneal ulcer – cultured – no org – cleared + antibiotics
10. corneal ulcer – cultured – Staph – R antibiotics – cleared
11. Cultured fungal Keratitis – aspergillus – initially fungicide after R + pimaricin
12. Keratitis – cultured – no org – R antibiotics – cleared
13. Keratitis – cultured – no org – R antibiotics – cleared
14. Keratitis – cultured – no org – R antibiotics – cleared
15. Cultured Keratitis – Ac org on culture R antibiotics 1st week – cleared – cleared after 3 months R/

16. Keratitis – Ac org on culture – R antibiotics – cleared
17. Keratitis – cultured ac org – R antibiotics – cleared
18. Keratitis – cultured – ac org – R antibiotics – cleared
19. Keratitis – cultured ac org – R/ Combo – cleared
20. Recurrent Keratitis – cultured – diphtheroids – R antibiotics – cleared
21. Keratitis – cultured – no org – R antibiotics – cleared
22. Keratitis – cultured – no org – cleared + antibiotics – R corneal scar 7 months after PKP
23. corneal ulcer – cultured – diphtheroids – cleared + antibiotics
24. Keratitis – cultured – no org – cleared + antibiotics
25. Keratitis – cultured – diphtheroids – cleared + antibiotics
26. Keratitis – cultured – no org – cleared + antibiotics
27. Keratitis – Ac. R+ gram + on culture – cleared + antibiotics
28. corneal ulcer – cultured diphtheroid + candida albicans – fungicide – deep fungal
29. corneal ulcer – Staphylococcus – R+ antibiotics – pinpoint leukoma
30. Keratitis – cultured – no org – cleared + antibiotics
31. Keratitis – Candida – diphtheroid – cleared + antibiotics

Corneal ulcer

52	Keratitis -	culture - no org -	½ antibiotics -	cleared
53	Keratitis -	culture - staphylo	cleared & antibiotics	
54	Corneal ulcer	culture - Pseudomonas	cleared & antibiotics	
56	Keratitis -	no growth	cleared & antibiotics	
57	Corneal ulcer	no growth	½ antibiotics	surgical treatment
58	Keratitis	culture - staphylo	½ antibiotics	cleared
59	Keratitis	culture - no org	½ antibiotics	cleared
60	Keratitis	culture - no org	½ antibiotics	cleared
61	Corneal ulcer	culture - pseudomonas	cleared & antibiotics	
62	Keratitis	no growth	½ antibiotics -	healed
63	Keratitis	culture - org	½ Combo -	cleared
65	Keratitis	culture - staphylo	½ antibiotics	cleared
66	Keratitis	no growth	½ antibiotics -	healed
67	Corneal ulcer	culture - Serratia Marcescens	antibiotics &	transplant
68	Keratitis	neg culture	antibiotics -	cleared
69	Keratitis	culture - Staph	antibiotics -	cleared
70	Keratitis	no growth	Antibiotics -	cleared
71	Keratitis	culture - neg	Combo -	cleared
72	Corneal ulcer	Staph	Combo -	Cleared
73	Keratitis	no growth	Combo -	cleared
74	Keratitis	culture staphylo	antibiotics -	healed
75	Keratitis	staphylo	antibiotics -	cleared
76	Keratitis	no growth	antibiotics -	cleared
77	Keratitis	culture - neg	½ antibiotics	cleared
78	Keratitis	culture - neg	½ Combo prep -	cleared
79	Keratitis	culture - neg	½ antibiotics	cleared
80	Corneal ulcer	culture - Staph -	½ antibiotics -	fully transplant
81	Keratitis	culture - staphylo	mild & antibiotics	
82	Keratitis -	Culture - neg	½ antibiotics - no response - scrubbed to steroid - no organ after 3/c all med + bx/p & AMA - clear (2 3 days)	
83	Corneal ulcer	culture - fungus	½ Aspergillus fl -	transplant
84	Keratitis	culture - staphylo	½ Antibiotics - no response	Combo - Cleared 8 days
85	Keratitis	no growth	½ antibiotics -	cleared

65	Corneal ulcer - central	culture	Pseudomonas	R antibiotics - central healing ulceral thinned
66	Keratitis	neg culture		R antibiotics - cleared
67	Keratitis	culture - ophthalmol.		R antibiotics - cleared
68	fungal ulcer	culture aspergillus		L primarion - cleared & painful scar
69	Keratitis	neg culture		R Combo - cleared
70	Keratitis	culture - neg		Antibiotics R cleared
71	Keratitis	culture - neg		R antibiotics - cleared
72	Keratitis	culture - neg		R antibiotics - cleared
73	Keratitis	culture - neg		antibiotics - cleared
74	Keratitis	culture - diphtheroids		Combo - no response in 5 days
				switched to antibiotics cleared in 4 days
75	Keratitis	culture - neg		R antibiotics - cleared
76	Keratitis	neg culture		antibiotics - cleared
77	Keratitis	culture - neg		antibiotics - cleared
78	Keratitis	culture - neg		antibiotics - cleared
79	Keratitis	neg - culture		R antibiotics - cleared
80	Corneal ulcer - perforated	Staph - positive		Antibiotics cleared - scar
81	Keratitis	neg - culture		Antibiotics - R cleared
82	Keratitis	neg - culture		Combo - cleared
83	Keratitis	neg - culture		antibiotics cleared
84	Keratitis	culture - diphtheroids		antibiotics cleared
85	Keratitis	culture - neg		antibiotics R cleared
86	Corneal ulcer	fungal culture - later Pseudomonas		Fusarium corneal transplant
87	Keratitis	culture - neg		antibiotics cleared
88	Keratitis	culture - neg		antibiotics cleared
89	Corneal ulcer	Pseudomonas - Culture		antibiotics - scar - transplant
90	Keratitis	culture - neg		antibiotics cleared
91	Keratitis	culture - diphtheroids		R antibiotics cleared
92	Keratitis	neg - culture		R antibiotics cleared
93	Corneal ulcer - atopic	Staph - culture		Antibiotics - transplant
94	Keratitis	neg - culture		R antibiotics cleared
95	Corneal ulcer	culture - Pseudomonas		R antibiotics - scar - transplant (2 times)
96	Keratitis	culture - neg		L antibiotics - cleared

97	Kanbkhs	culture neg	Rx antibiotics	cleared
98	ulcer	Pseudomonas	Rx antibiotics	transplant
99	kanbkhs	culture neg	Rx antibiotics	cleared
100	Kanbkhs	neg culture	Rx antibiotics	cleared
101	Kanbkhs	neg culture	Rx antibiotics - 3 weeks - NO drops added Steroids - began to get better in 10 days - Rx	
102	kanbkhs	neg culture	antibiotics	cleared
103	Kanbkhs	neg culture	antibiotics	cleared
104	Kanbkhs	neg culture	antibiotics	cleared
105	corneal ulcer	didn't remember what culture was but was +	Rx antibiotics -	transplant
106	Kanbkhs	Staphylococcus	antibiotics	cleared
107	Kanbkhs	neg culture	antibiotics	cleared
108	corneal ulcer	Pseudomonas	antibiotics	transplant
109	Kanbkhs	staphylococcus	antibiotics	steroid keratoplasty needed
110	kanbkhs	neg culture	antibiotics	cleared
111	kanbkhs	didn't remember what culture was but was +	antibiotics -	playful ocean
112	corneal ulcer	neg culture	antibiotics	cleared
113	kanbkhs	Pseudomonas	antibiotics	transplant
114	corneal ulcer	neg culture	antibiotics	cleared
115	kanbkhs	culture - pseudomonas (anaerobic neg)	antibiotics	transplant
116	corneal ulcer	neg culture	antibiotics	cleared
117	Kanbkhs	Staph	antibiotics	transplant
118	corneal ulcer	neg culture	antibiotics	cleared
119	kanbkhs	neg culture	antibiotics	cleared
120	kanbkhs	neg culture	antibiotics	cleared
121	kanbkhs	neg culture	antibiotics	cleared
122	kanbkhs	staphylococcus	antibiotics	cleared
123	kanbkhs	neg culture	antibiotics	cleared
124	kanbkhs	neg culture	antibiotics	cleared
125	kanbkhs	Positive culture - mixed (doesn't remember what)	antibiotics	cleared
126	kanbkhs	neg culture	antibiotics	cleared
127	kanbkhs	neg culture	antibiotics	cleared
		neg culture	antibiotics	cleared

128	coral color	fungal culture		
129	Kirby	culture - neg		cleared
130	Kirby	culture - neg		cleared
131	Kirby	Ophthal - neg culture		cleared
132	Kirby	neg culture		cleared
133	Kirby	neg culture		cleared
134	coral color	Staph		
135	coral color			
136	Kirby	neg culture		
137	Kirby	neg culture		cleared
138	coral color	culture neg		cleared
139	Kirby	neg culture		cleared
140	Kirby	culture neg		cleared
141	Kirby	neg culture		
142	Kirby	neg culture		
143	Kirby	Ophthalmic		cleared
144	Kirby	neg culture		cleared
145	Kirby	culture neg		cleared
146	Kirby	neg culture		cleared
147	Kirby	neg culture		cleared
148	coral color	neg culture		
149	Kirby	neg culture		
150	Kirby	neg culture		cleared
151	coral color	culture - Staph		cleared
152	coral color	fungal culture		
153	coral color			
154	Kirby	neg culture		
155	Kirby	Ophthalmic		cleared
156	Kirby	gram culture -		cleared
157	Kirby	neg culture		cleared
158	Kirby	culture neg		cleared
159	Kirby	neg culture		cleared
160	Kirby	Ophthalmic		cleared
161	Kirby	neg culture		cleared

162	Kimbrough	outlaw - slightly	B outlaw	closed	
163	Kimbrough	outlaw - very	L outlaw	closed	
164	Kimbrough (outlaw)	outlaw - very OL	R outlaw	closed	
165	Kimbrough	slightly	R outlaw	closed	
166	Kimbrough	slightly	R outlaw	closed	
167	Kimbrough	outlaw - very	outlaw	closed	
168	Kimbrough	very - outlaw	outlaw	closed	
169	Kimbrough	very outlaw	outlaw	closed	
170	Kimbrough	very outlaw	outlaw	closed	
171	Kimbrough	very outlaw	outlaw	not eligible for 3 days - outlaw closed else in 6 days	
172	Kimbrough	very outlaw	outlaw	closed	
173	Kimbrough	slightly	outlaw	closed	
174	Kimbrough	very outlaw	outlaw	closed	
175	Kimbrough	outlaw - very	outlaw	closed	
176	Kimbrough	outlaw - very	outlaw	closed	
177	Kimbrough	outlaw - very	outlaw	closed	
178	Kimbrough	outlaw - very	outlaw	closed	
179	Kimbrough	very outlaw	Combo	closed	
180	Kimbrough	very - outlaw	outlaw	closed	
181	Kimbrough	for outlaw - slight	outlaw very outlaw	closed but : overnight	
182	Kimbrough	very outlaw	outlaw	closed	
183	Kimbrough	outlaw - very	outlaw	closed	
184	Kimbrough	all outlawed offers on outlaw very	outlaw	closed on special ground -- D/C 9 put owner -- D/C outlawed on outlawed offer got letter outlawed for 3 days	
185	Kimbrough				
186	Kimbrough				
187	Kimbrough				
188	Kimbrough	very outlaw	outlaw - closed		
189	Kimbrough	very outlaw	outlaw - closed		

196	neg culture	? antibiotics	cleared
197	culture - neg	antibiotics	cleared
192	neg culture	antibiotics	cleared
193	culture neg	antibiotics	cleared
194	neg culture	antibiotics	cleared
195	neg culture	antibiotics	cleared
196	neg culture	antibiotics	cleared
197	gram neg rods	antibiotics	cleared - purpled clear
198	neg culture	antibiotics	cleared
199	neg culture	antibiotics	cleared
200	neg culture	COMBO	cleared - purpled around the
201	fungus - aspergillus	heterogenic	cleared - purpled clear
202	neg culture	antibiotics	cleared
203	culture - neg	antibiotics	cleared
24	neg culture	antibiotics	cleared - [illegible]
205	culture neg	antibiotics	cleared
206	neg culture	antibiotics	cleared
207	neg culture	antibiotics	cleared
208	Pseudomonas	antibiotics -	transplant
209	neg culture	antibiotics	cleared
210	Staph	antibiotics	cleared
211	Steroids Mucormycosis	antibiotics	leukemia - no transplant [illegible]
212	neg culture	antibiotics	cleared
213	neg culture	antibiotics	cleared
214	neg culture	antibiotics	cleared
215	doesn't matter long	antibiotics	purpled leukemia cell
215'	neg culture	antibiotics	cleared
216	neg culture	antibiotics	cleared
217	Pseudomonas	antibiotics	transplant
218	neg culture	antibiotics	cleared

Sent to MAI

219	Pseudomonas - neg	? antibiotics	leukemia - neural agnes
220	Pseudomonas - neg [illegible]	? antibiotics	leukemia - purpling
221	Pseudomonas - neg culture	? antibiotics	transplant
222	neg Pneumococcus	? antibiotics	cleared
223	Pseudomonas - neg [illegible]	? antibiotics	cleared
224	neg - neg	? antibiotics	cleared
225	neg - neg	steroid-antibiotics - combo	cleared
226	Pseudomonas - neg [illegible] not cultured	antibiotics	cleared
227		? antibiotics	cleared
228		antibiotics	marked leukemia
			purpled leukemia

EDS
5-8-80

Mr. GORE. Why did you have to put it into the big notebook?

Dr. SCAFIDI. A controversy came up about salt tablets about that time. A lawyer called me on the phone and said he never heard of an adverse reaction to a salt tablet. I told him I talked to a lot of individuals and I had some. He insisted he never saw any. I said, "Well, this is as good a time as any in the fall of the year to put this thing together." So I did.

Mr. GORE. You took 3 years' worth of small notebooks and transcribed the data into the large notebook?

Dr. SCAFIDI. Yes.

Mr. GORE. Why did you change pens every three or four entries?

Dr. SCAFIDI. I didn't even pay attention to that until now I noticed it.

Mr. GORE. Did you have a pile of pens next to you?

Dr. SCAFIDI. I do have a pile of pens on my desk. I certainly do.

Mr. GORE. Was it your practice to write a few entries with one pen and then put that pen down and choose one with a noticeably different ink color and make a few other entries?

Dr. SCAFIDI. I probably did.

Mr. GORE. Is that probably the way you did it?

Dr. SCAFIDI. Probably.

Mr. GORE. It is apparent that you used at least five different pens and four different colors of ink. It appeared that either the color of ink and/or the pen was changed 20 times in the recording of this large notebook.

However, your testimony is that you sat down and transcribed 3 years' worth of data that had been put into smaller notebooks. That does not make sense, Doctor.

Dr. SCAFIDI. Why doesn't it? I get a tremendous number of phone calls. If I stop to do something else and come back to my notebook, or maybe set it aside to go to lunch or a meeting, I come back and pick up the first pen that is close to me.

Mr. GORE. I think I should advise you again at this point that your testimony here today before this subcommittee is under oath. You are running the danger of perjury if you give false responses to questions put to you.

Dr. SCAFIDI. That's right.

Mr. GORE. You are telling us a story that is impossible for a reasonable person to believe. You are telling us that you compiled 3 years' worth of reports given you by doctors who were afraid to give their names, and you didn't get any of the relevant data associated with these reports. Then you took all these small notebooks and sat down and compiled the data in a larger notebook and changed pens every few entries.

A reasonable person might conclude that this large notebook was fabricated by you in response to persistent pressure from people who were having to pay too much money for this substitute product, and that you used this fabricated notebook to justify the earlier decision. Is that a fair conclusion?

Dr. SCAFIDI. To me it is not.

Mr. GORE. Is that what you did?

Dr. SCAFIDI. No.

Mr. GORE. Can you give us one doctor's name as a source of any of the reports that you filed in this notebook?

Dr. SCAFIDI. No, I can't do that under the Privacy Act.

Mr. GORE. Can you give us one patient's name?

Dr. SCAFIDI. No, I cannot give you that. I didn't collect patients' names. I just simply asked for things, of the doctors, "Did you have a problem with the salt tablet? What was it? Did you culture it?" Again, the notebook was simply for my own information to find out if indeed there was a problem, and if there was to pursue it further.

Mr. GORE. Congress is exempt from the Privacy Act. Let me advise you that there are no Privacy Act problems with the release of that data to this subcommittee. There is no problem at all. Give us one doctor's name, if there is a doctor.

Dr. SCAFIDI. Well, of course, Dr. Louis Wilson at Emory University is one doctor.

Mr. GORE. How many of the 200 reports did he give you?

Dr. SCAFIDI. No more than one or two at the most.

Mr. GORE. Give me another doctor's name.

Dr. SCAFIDI. Offhand I just can't. I don't remember doctors' names. I have a very hard time remembering people in my own division's names.

Mr. GORE. If you have problems remembering doctors' names, why don't you write their names down in your notebook?

Dr. SCAFIDI. Because I wasn't looking for doctors' problems. I was looking for salt tablet problems for my own interest.

Mr. GORE. What about patients' names?

Dr. SCAFIDI. Rarely do we ever discuss problems by patients' names.

Mr. GORE. On April 18 you turned over your notebook for the first time to the Bureau of Medical Devices. Is that correct?

Dr. SCAFIDI. Bureau of Medical Devices had the notebook sooner than that. Dr. Talbert asked me for it. I never sent a memo with it. I sent it to him for his own information.

Mr. GORE. When?

Dr. SCAFIDI. I believe in March. He asked me for a memo and I wrote him a memo.

Mr. GORE. April 18.

Dr. SCAFIDI. Yes.

Mr. GORE. At the time of the April 18 memo there were 218 entries in your notebook. That was on a Friday, was it not?

Then on the following Monday there were 226 entries in the notebook. Was there a sudden epidemic of eight problems over the weekend? Did your phone ring a lot over the weekend?

Dr. SCAFIDI. I don't remember whether I had another notebook and added to it or what, but I did add some additional ones to it.

Mr. GORE. Over the weekend. Why did you add the additional eight over the weekend? Were those telephone calls? Did you attend a convention that weekend?

Dr. SCAFIDI. I don't remember.

Mr. GORE. It is the subcommittee's conclusion that you were in town that weekend. Do you remember any telephone calls that might account for the eight entries in that 3-day period?

Dr. SCAFIDI. I do not remember.

Mr. GORE. Four of those eight entries were about pseudomonas. Is that correct? That is a 50-percent occurrence of pseudomonas in those entries. That is a very rare and serious infection.

Dr. SCAFIDI. People don't call me about their good results or don't talk to me about good results.

Mr. GORE. When they called you, or when they allegedly called you, for entries Nos. 1 through 196, there were for those 196 cases 10 pseudomonas—or an incidence of 5 percent. Over that weekend you had eight adverse reactions reported to you and four cases of pseudomonas, or an incidence of 50 percent.

How do you explain that?

Dr. SCAFIDI. I don't remember the weekend, or I don't remember all the circumstances. Certainly prior—I don't recall the date, but in the last year the incidence of salt tablet use has increased. You can look in the ophthalmologic journals and see salt tablets advertised. Patients more and more are using salt tablets. One would expect an increase in problems associated, if indeed there was a problem.

The other thing is that I would expect doctors to be calling me more if they had problems.

The other thing is that for the last 5 years I have spent a lot of time in public relations trying to get doctors to call me when they have problems.

Mr. GORE. That is another curious feature of this testimony. That is, how all of these hundreds of doctors around the country know your home telephone number and know that you are the person that they ought to call if they have a problem related to salt tablets. How do you suppose all these doctors around the country have come to identify you as the person that they ought to call, some of them muffling their voices, to report problems associated with salt tablets?

Dr. SCAFIDI. Well, first of all, unfortunately I am the only ophthalmologist in the Bureau of Drugs. There is no ophthalmologist there.

I have been to quite a few meetings. I have been interviewed on numerous occasions, quoted in newspapers, and my telephone number is in the phone book.

Mr. GORE. Mrs. Bruch, do you believe this testimony?

I would advise counsel that consultations concerning constitutional rights are permissible. Otherwise under the House Rules an attorney is not permitted to coach a witness.

Mrs. Bruch, do you believe this testimony?

Mrs. BRUCH. Within limits, yes.

Mr. GORE. What are the limits to your belief?

Mrs. BRUCH. I just don't know—you know, somebody tells you something and you can only judge how often this happened or what. I do recall the two cases that I recall Dr. Scafidi specifically mentioning to me because I have been interested in anaerobic bacteria, and these were the instances where they had streptococci, anaerobic streptococcus. Other than that, I just don't get into the clinical aspects of this.

Mr. GORE. You have listened to his testimony here this morning and his responses to the questions. Do you think a reasonable person would believe this was done this way?

Mrs. BRUCH. It is reasonable.

Mr. GORE. You believe it is reasonable?

Mrs. BRUCH. I think it is reasonable. I would only add the comment that in my experience in dealing with both optometrists and ophthalmologists, primarily these infections would occur with ophthalmologists, it is that they are very hesitant to tell you about serious eye problems and have great hesitancy to report them to our agency.

Mr. GORE. Has he talked with you on numerous occasions about the large number of health problems that have been reported to him concerning salt tablets?

Mrs. BRUCH. He has mentioned—I gave you the specific instance that I recall.

Mr. GORE. One?

Mrs. BRUCH. On the streptococcal infections, and he had mentioned that he had other people call him.

Mr. GORE. But the other 200 occasions were not mentioned?

Mrs. BRUCH. I was not aware of the numbers.

Mr. GORE. Let me recognize Mr. Lent.

Mr. LENT. Thank you, Mr. Chairman.

I would like to pick up a line of questioning to Dr. Scafidi regarding the notebook, the pocket notebook, and so forth. Doctor, do you use these pocket notebooks only when you travel or do you also use them when you are here in town?

Dr. SCAFIDI. I use them both times.

Mr. LENT. When do you make the transfer of the data from these small notebooks into the large notebook? Do you do it after you complete a trip? Do you wait a while? How do you do it?

Dr. SCAFIDI. I have no other notebooks right now except the one little one.

Mr. LENT. You threw all the other little ones away.

Dr. SCAFIDI. I have no use for them.

Mr. LENT. When do you make the transfer from the small notebooks into the large notebooks—immediately after you come back from a trip? Do you leave it around a week or two? How do you do that?

Dr. SCAFIDI. Most of the time I leave it around except when this controversy came up. When I got things I put them in sooner.

Mr. LENT. So for 4 years now you have been maintaining these small notebooks.

Dr. SCAFIDI. Right.

Mr. LENT. And there came a time—and I will ask you when—you transferred that information from the small notebooks into the large notebook.

Dr. SCAFIDI. Right.

Mr. LENT. Can you tell us when that was?

Dr. SCAFIDI. The last quarter, August, September, October, that time of the year last year.

Mr. LENT. You said earlier you had quite a supply of these small notebooks.

Dr. SCAFIDI. I surely did.

Mr. LENT. You finally threw them away.

Dr. SCAFIDI. Yes.

Mr. LENT. Do you recall when that was?

Dr. SCAFIDI. Right after I put them in the big one.
Mr. LENT. When was that?
Dr. SCAFIDI. August, September, October, around in there.
Mr. LENT. So you must have had quite a pile of them at the time you transferred them. You didn't just have one but you had more than one.
Dr. SCAFIDI. I had more than one.
Mr. LENT. How many did you have?
Dr. SCAFIDI. I never counted them.
Mr. LENT. More than 5, more than 10, less than 20?
Dr. SCAFIDI. I have no idea.
Mr. LENT. But there was a pile of them?
Dr. SCAFIDI. Yes.
Mr. LENT. You sat down at one sitting and put them in the large notebook?
Dr. SCAFIDI. I don't think it was one sitting. I don't remember. It just came and went. I just put them together.
Mr. LENT. Yet you used these different colored inks?
Dr. SCAFIDI. Right. I don't check the color. I happen to be a nut on colored pens.
Mr. GORE. Excuse me. Did you say you happened to be a nut on colored pens?
Dr. SCAFIDI. Yes.
Mr. GORE. Is it your common practice to change pens? If you write a letter, for example, do you use different colored pens throughout the text of the letter?
Dr. SCAFIDI. I haven't written a personal letter in so long I don't really remember.
Mr. GORE. Have you used a pencil several times? Are you a nut on pencils, also?
Dr. SCAFIDI. I most certainly am.
Mr. GORE. Thank you.
Mr. LENT. How many different clinicians furnished you—just a ball park figure—with these 228 entries of adverse reaction reports, as you call them?
Dr. SCAFIDI. Mr. Lent, I don't remember. I talked to so many——
Mr. LENT. 228 different clinicians, or did some call you more than once?
Dr. SCAFIDI. I don't remember.
Mr. LENT. Were there more than 5, less than 10?
Dr. SCAFIDI. More than 5 or less than 10 what?
Mr. LENT. Clinicians. We want to know how many different clinicians gave you these adverse reaction reports. There are 228 entries.
Dr. SCAFIDI. I just don't remember how many. I don't remember whether I got more than one, from numerous, or what.
Mr. LENT. Why did you not identify them in your notebook?
Dr. SCAFIDI. I had no need to identify them.
Mr. LENT. You indicated earlier that you thought there was something privileged about the names of these physicians.
Dr. SCAFIDI. I was under the impression that we can't use information when we mention a doctor's name. That is his privacy. If he wants to talk to me privately about a problem he should have that privilege without fear of being quoted.

Mr. LENT. Where the patient is not identified, certainly you don't believe there is a privilege involved in the name of the doctor.

Dr. SCAFIDI. That never even crossed my mind.

Mr. LENT. Why were the ages and sexes of the patients represented in the 226 entries not recorded?

Dr. SCAFIDI. Because I never asked it.

Mr. LENT. You are familiar with the registry of drug-induced ocular side effects maintained by the University of Oregon?

Dr. SCAFIDI. Yes, sir.

Mr. LENT. Does that not require this information, the age of the patient and the sex of the patient be recorded, and the name of the physician?

Dr. SCAFIDI. Dr. Gardner has read the contract in the registry of drug-induced ocular side effects. In that contract there is no requirement for them to keep a list of any data on ophthalmic devices. It is strictly drugs. It was ophthalmic devices one year, a $10,000 ad for one year. The Bureau of Devices discontinued the devices part of the registry.

Mr. LENT. Do you maintain that tablets are a device and not a drug?

Dr. SCAFIDI. That is exactly right. They are an adjunct to a device. That is how the Bureau calls it. Anyway, I asked the people in Oregon if they got any data on devices, if they would keep it up for me and report it for me separately to see what was going on, if anything was. They said they would as a favor.

Mr. LENT. Why did you wait until you had 196 adverse reactions to report before advising the registry at the University of Oregon in 1979?

Dr. SCAFIDI. Because the registry at that time was not collecting contact lenses or their adjunct reporting data. I asked them if they would do that. They said they would. I just happened to be—because as I said before I had been questioned about the contact lens and the salt tablet controversy, when I put my data together I decided to send it to the drug registry.

Mr. LENT. Is it not a fact that you were the project officer in a survey which required the doctor's name, the name of the patient, the patient's age, and the patient's sex, and the date of the reaction?

Dr. SCAFIDI. I was the project officer for the drug-induced ocular side effects contract. You will note that every one of those things was voluntary. The doctor did not have to put his name if he did not want to.

Mr. LENT. In every one of these cases the doctor voluntarily decided not to give the name?

Dr. SCAFIDI. The doctor's name had to be removed just like in my present contract. We do not receive the doctor's name when we collect the data from the University of Oregon. We received the adverse reaction.

When that survey came in I got a printout of it but most of it went to the Bureau of Devices because they were going to analyze it themselves.

Mr. LENT. Do you keep the doctor's name on file?

Dr. SCAFIDI. I don't get the doctor's name from the University of Oregon project.

Mr. LENT. Doesn't the registry get the doctor's name?

Dr. SCAFIDI. No, they cannot by contract.

Mr. LENT. Let us change to another subject. Perhaps Chairman Gore will pick up on that in a few moments.

In June of 1976, Dr. Finkel issued a memorandum. This memorandum called for the relabeling of salt tablets. Are you familiar with that memorandum?

Dr. SCAFIDI. I don't remember.

Mr. LENT. Perhaps it can be shown to Dr. Scafidi. It is exhibit No. 3 of the salt tablet chronology. [See p. 67.]

Are you familiar with that? After looking it over does it refresh your reaction? Have you ever seen that document before?

Dr. SCAFIDI. I believe I have seen this memo before.

Mr. LENT. You see in that memorandum where the instruction is given that the salt tablets should be labeled as clearly secondary to the use of preserved saline solutions and to be reserved for use only while traveling when preserved saline solutions may be difficult to acquire. Did you work on notices for the relabeling of saline tablets to go into the Federal Register?

Dr. SCAFIDI. I don't remember it. I remember this memo now that I look at it.

Mr. LENT. Mrs. Bruch, you are familiar with this memorandum, are you not?

Mrs. BRUCH. Yes. Do you have the other portion of the memorandum dated May 24, 1976? That is the initiating memo. What you have is the response to that memo. I will be glad to give you this copy.

Mr. LENT. Yes, we do have it here. [See p. 59.]

Mrs. BRUCH. I prepared that memo.

Mr. LENT. You prepared this memo?

Mrs. BRUCH. Yes.

Mr. LENT. What I was trying to determine is, why was no action taken with respect to notices being put in the Federal Register for the relabeling of these salt tablets.

Mrs. BRUCH. The fact that at least I was pursuing was to have the salt tablets replaced with preserved saline.

Mr. LENT. We know that. You wanted to have the salt tablets replaced. Here is Dr. Finkel saying to you that you will not replace them completely. You should simply initiate action to have salt tablets relabeled. Apparently, unless I am mistaken, you can straighten me out if I am, no one ever did any work——

Mrs. BRUCH. To be used as a secondary means. We were constantly faced with the problem of what—and it is in the labeling of most solutions—as to what you tell a patient who does not have—he goes away for the evening and does not return home and does not have any solution—what do you tell them to do? We have several instances in which it is in the labeling to use a pan of boiling water.

Mr. LENT. All that is very interesting.

Mrs. BRUCH. This is what that is——

Mr. LENT. 1976—more than 4 years ago.

Mrs. BRUCH. That is correct.

Mr. LENT. Calling for publication in the Federal Register of relabeling notices for salt tablets. You never moved forward on that?

Mrs. BRUCH. We did not.

Mr. LENT. Why not?

Mrs. BRUCH. The indication is to label them as emergency use. We did not do that.

Mr. LENT. Why not?

Mrs. BRUCH. Because we were working on the commitment to replace the salt tablets.

Mr. LENT. It does not say emergency use, but secondary use—salt tablets should be relabeled for secondary use.

Mrs. BRUCH. I consider that when it is not routine use.

Mr. LENT. You are aware, are you not, that consumers did not have notice of this withdrawal until they were no longer available on the market?

Mrs. BRUCH. That is correct.

Mr. LENT. Is it not the function of the Federal Register to provide notice to the public?

Mrs. BRUCH. It is to provide notice to the public. I am not sure that it is for every instance where I would believe or the agency believes that there is a serious risk to health.

Mr. LENT. Bausch and Lomb has told the subcommittee staff that back in 1976 they got the impression from the FDA that you wanted the salt tablets off the market.

Mrs. BRUCH. Pardon me, Mr. Lent. What was the date?

Mr. LENT. 1976.

Mrs. BRUCH. Yes.

Mr. LENT. Roughly at the same time that this memo was issued by Dr. Finkel.

Mrs. BRUCH. I had discussed the difficulties associated with salt tablets which are more than the infection problems, certainly not as serious as that, but I discussed it during 1974 and 1975, so it is not limited to 1976.

Mr. LENT. Dr. Scafidi, you had conversations with Bausch & Lomb that indicated to them, or reasonably were intended to indicate to them, that you wanted these salt tablets off the market?

Dr. SCAFIDI. Most all of the meetings were held in a group. It was not individually.

Mr. LENT. What did you tell the group with respect to salt tablets and getting them off the market, if anything?

Dr. SCAFIDI. Frankly I don't remember.

Mr. LENT. You don't remember?

Dr. SCAFIDI. That is right.

Mr. LENT. Your recommendation on July 19, 1976, in your medical office's review of annual report, stated: "Adverse reactions were low but must be carefully monitored." Do you recall making that statement? You put it in a memorandum. [See p. 72.]

Dr. SCAFIDI. July 19, 1976?

Mr. LENT. That is right. That can be furnished to you.

Dr. SCAFIDI. I don't find it.

Mr. LENT. Do you find it? There you are on July 19, 1976, making a statement in this report: "Adverse reactions were low but must be carefully monitored." You were referring to salt tablet

use. My question is this: What occurred to prompt you & Mrs. Bruch, who I think was also present, then to meet with Bausch & Lomb on December 9, 1976, and obtain a commitment from Bausch and Lomb that it would remove the salt tablets from the market? Do you recall receiving that commitment?

Dr. SCAFIDI. Mr. Lent, this here is in relation to all adverse reactions. I don't even see the words "salt tablet" mentioned in this medical officer's annual report review. I just said I feel the incidence of adverse reaction is low and must be carefully monitored.

Mr. LENT. That would be from all sources that adverse reactions were low.

Dr. SCAFIDI. That is right, exactly.

Mr. LENT. That was in 1976.

Dr. SCAFIDI. July 1976.

Mr. LENT. At that time everyone who had soft contact lenses was using salt tablets. Is that not correct?

Dr. SCAFIDI. No, sir. The other companies that had soft contact lenses on the market at that time did not have that.

Mr. LENT. What percentage were using the salt tablets in 1976 in your opinion?

Dr. SCAFIDI. I don't know if I can give you a percentage.

Mr. LENT. It had to be a very high percentage.

Dr. SCAFIDI. It was a large number; high, yes.

Mr. LENT. Ninety to ninety-five percent? Would that be an unfair estimate of the number using that? There was only one approved saline solution on the market at that time. Is that right?

Dr. SCAFIDI. That is right.

Mr. LENT. That was the Burton-Parsons.

Dr. SCAFIDI. Boil and soak.

Mr. LENT. They had a very small share of the market?

Dr. SCAFIDI. More than likely. Yes, they did have a small share of the market.

Mr. LENT. They were the only ones who had the prepared saline solution in 1976?

Dr. SCAFIDI. That is right.

Mr. LENT. So it is fair to say that an overwhelmingly large proportion of the maintenance of soft contacts was carried out, in 1976 at least, by the use of salt tablets.

Dr. SCAFIDI. Probably.

Mr. LENT. You said that adverse reactions were low but must be carefully monitored.

Dr. SCAFIDI. That is right.

Mr. LENT. You cannot remember the share exactly. Would you say 90 percent was a fair estimate?

Dr. SCAFIDI. I guess by that time they had 10 percent of the market. I am not in the marketing end of things.

Mr. LENT. Within 5 months after you wrote that memo, or that report, you got salt tablets off the market, did you not?

Dr. SCAFIDI. They were taken off the market.

Mr. LENT. You got a commitment from Bausch & Lomb to get them off the market, did you not?

Dr. SCAFIDI. Yes, sir.

Mr. LENT. Why? If you made a report in which you said the incidence of trouble was low, why did you then pursue the matter

and within 5 months get a commitment from Bausch & Lomb, which they implemented, to get salt tablets off the market?

Dr. SCAFIDI. It was a potential problem of infection which was still there. The problem with not getting the right water, discoloration of the lens due to the water, improper making of solution. That problem was still there.

Mr. LENT. Do you know a man named Chet Laufer?

Dr. SCAFIDI. Chet Laufer. I sure do. I have known him about 6 years.

Mr. LENT. Did he work for Bausch & Lomb at that time?

Dr. SCAFIDI. Bausch & Lomb, no.

Mr. LENT. Burton-Parsons?

Dr. SCAFIDI. Yes.

Mr. LENT. Would you describe your relationship with him?

Dr. SCAFIDI. Chet and I are good personal friends.

Mr. LENT. Does he in his capacity as a drug representative have occasion to give you samples, and so forth, in private practice?

Dr. SCAFIDI. I never have gotten samples from Chet, no.

Mr. LENT. Have you ever shared a hotel room with him?

Dr. SCAFIDI. I sure have.

Mr. LENT. At conventions, and so forth?

Dr. SCAFIDI. That is right. I paid my half of the room.

Mr. LENT. Where were they?

Dr. SCAFIDI. San Francisco.

Mr. LENT. What hotel was it? Do you recall? Was it the St. Francis?

Dr. SCAFIDI. I don't remember the hotel name.

Mr. LENT. If I told you it was the St. Francis, does that refresh your recollection?

Dr. SCAFIDI. I take your word for it. I would have to go back and look at my travel order.

Mr. LENT. Let me ask you this—why would you, a Federal employee, a regulator, why would you share a room with a representatives of a regulated industry under your jurisdiction?

Dr. SCAFIDI. I came up from Newport Beach. It is very difficult to get a room at an ophthalmic convention, particularly the American Academy of Ophthalmology. I blew into town and didn't have a room. I called Chet. Chet said I could share the room with him. I did.

Mr. LENT. Did you clear that room arrangement with your supervisor, Dr. Gibson?

Dr. SCAFIDI. I asked him in the past if I could do that. He does not recall that request.

Mr. LENT. Do you think Dr. Gibson would corroborate that?

Dr. SCAFIDI. He doesn't recall the request. I am sure he would corroborate it. He told me he did.

Mr. LENT. Do industry representatives make reservations for you at hotels in the company name, do you know?

Dr. SCAFIDI. I don't recall. I really don't. I was asked that question the other day. I couldn't remember.

Mr. LENT. Mr. Chairman, I would like to defer my further questions until a later time.

Mr. GORE. Thank you very much.

Let me return to this registry briefly. Then I have another series of questions.

In your report to the registry, Dr. Scafidi, you said, "All 196 of these incidents, the case and the lens as well a the patients' eyes, were cultured." How did you know that?

Dr. SCAFIDI. The people I got the information from told me that. I usually ask that.

Mr. GORE. You usually ask that?

Dr. SCAFIDI. Yes.

Mr. GORE. You neglected to ask the name of the doctor or the age or sex of the patient, but you did ask whether the eye was cultured?

Dr. SCAFIDI. In an eye infection the age and sex of the patient is not that important. The important thing is what was the infection and what can be done about it.

Mr. GORE. At this point I would like to cite a memo from Mr. Edward Melton of the FDA's Office of Legislative Affairs [see p. 49] which states: "Dr. Scafidi pointed out that it is practically impossible to get ophthalmologists to culture an infected eye condition."

How do you explain that contradiction?

Dr. SCAFIDI. Routine conjunctivitis is almost impossible to get into culture. When you get an ulcer or something like that they will culture it. Some men are very energetic about culturing. Most of them are not.

Mr. GORE. How many of the 200 were routine conjunctivitis?

Dr. SCAFIDI. I do not remember.

Mr. GORE. You do not remember a lot of things, Doctor.

Dr. SCAFIDI. A lot of years have gone by.

Mr. GORE. Excuse me?

Dr. SCAFIDI. A lot of years have gone by since that time.

Mr. GORE. And a lot of money has been spent by American consumers, I believe unnecessarily. You are responsible for it, along with others at FDA.

Let me return to your notebook. You told our staff in their interviews with you that you kept that notebook—do you still have it there, that brown one?

Dr. SCAFIDI. Yes.

Mr. GORE. That one there. You kept that particular notebook with you for 4 years. Did you tell them that in your interviews?

Dr. SCAFIDI. If I did I was incorrect.

Mr. GORE. Let me call to the witness stand—if you would just stand behind these witnesses because I do not want them to move from the stand—Ms. Susan Leal, Ben Smethurst, former FBI agent working with the subcommittee, and Dr. Gardner.

Let me also ask Edward Melton, from the FDA, if you would come up and stand behind these witnesses.

Dr. Gardner, you can consider yourself still sworn.

Will the others raise your right hands and repeat after me?

Do you swear to tell the truth, the whole truth, and nothing but the truth, so help you God?

Ms. LEAL. I do.

Mr. SMETHURST. I do.

Mr. MELTON. I do.

Mr. GORE. Miss Leal, did Dr. Scafidi tell you that he kept that particular notebook for 4 years running?

TESTIMONY OF SUSAN LEAL, COUNSEL, AND BENJAMIN M. SMETHURST, SPECIAL ASSISTANT, SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS, COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE; AND EDWARD R. MELTON, OFFICE OF LEGISLATIVE AFFAIRS, FOOD AND DRUG ADMINISTRATION, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Ms. LEAL. Yes.

Mr. GORE. Did you pursue that point and confirm it in detail with him?

Ms. LEAL. Yes.

Mr. GORE. He insisted it was the same notebook?

Ms. LEAL. Yes.

Mr. GORE. And you asked him specifically whether he kept pieces of paper in small notebooks and transcribed it, and he insisted he kept that same notebook; is that correct?

Ms. LEAL. Yes. I was very curious about the new-looking nature of the notebook when I first saw it on April 21. Therefore, I discussed it in my first interview, but on the second interview I made a very specific point to ask him whether he had transferred it from other pieces of paper into that notebook.

I asked the question very slowly so that the two gentlemen with me would hear this question. He answered no, he did not transfer it from other pieces of paper, that he kept it in that notebook.

Mr. GORE. Mr. Smethurst, you were present at these meetings. Is it as Ms. Leal described it?

Mr. SMETHURST. I was present at the second meeting on May 6 and it is as she described it.

Mr. GORE. You are a former FBI agent. Is that correct?

Mr. SMETHURST. Yes.

Mr. GORE. You are quite used to conducting interrogations and interviews, and you believe you have a relatively good memory for what transpired during interviews?

Mr. SMETHURST. Yes.

Mr. GORE. Dr. Gardner, is that your recollection, also?

Dr. GARDNER. Yes, Mr. Chairman.

Mr. GORE. Mr. Melton, you were present at the second meeting, were you?

Mr. MELTON. I was present at the April 21 meeting.

Mr. GORE. The April 21 meeting?

Mr. MELTON. Not the second meeting.

Mr. GORE. That is the first meeting. Is that your memory of Dr. Scafidi's account?

Mr. MELTON. I do not recall that at the first meeting—we didn't talk about the notebook in great detail that I can recall.

Mr. GORE. The memo that I have prepared by you states, "Dr. Scafidi explained the running account of adverse reaction reports that he has personally listed in a notebook totalling some 226 cases, all of which were related to the use of salt tablets." Is that an accurate reading and your memory of that first meeting?

Mr. MELTON. Yes.

Mr. GORE. And the elaboration where you asked for details by Ms. Leal and Mr. Smethurst and Dr. Gardner at the second meeting, were you aware that his story was that he kept a running account in this notebook? Is that correct?

Mr. MELTON. Yes.

Mr. GORE. You are all excused. I would ask unanimous consent to put a memo in the record from Mark Raabe, chief counsel of the subcommittee, covering that information.

[The memorandum referred to follows:]

CONGRESS OF THE UNITED STATES
HOUSE OF REPRESENTATIVES
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS
OF THE
COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE
WASHINGTON, D.C. 20515

MEMORANDUM

June 25, 1980

TO: Chairman Eckhardt

FROM: Mark Raabe, Chief Counsel

SUBJECT: Dr. Arnauld Scafidi's Notebook
Food and Drug Administration

On May 8, 1980, the Subcommittee staff obtained from Dr. Scafidi a composition notebook which contains handwritten entries of 228 adverse reactions, listed numerically under a heading entitled "Infections of Patients Using Salt Tablets."

Dr. Scafidi voluntarily exhibited this notebook during interviews with the staff on April 21 and May 6, 1980. He advised that he has maintained the notebook for approximately four years and during that time has recorded in it information reported to him by doctors concerning adverse reactions experienced by patients using salt tablets for soft contact lens care. He stated that approximately 60 percent of the entries in the notebook were furnished to him by doctors at various professional meetings, and the remainder were reported to him by telephone, both at home and at work. In response to a specific question regarding the manner in which he maintains the notebook, Dr. Scafidi advised that he writes the data he receives directly in the notebook and that he does not record it elsewhere first and later transfer it into the notebook. He said that for this reason he has made it a practice over the years to have the notebook with him, whether he is at home, at work, or out of town.

Contrary to the information furnished by Dr. Scafidi, staff investigation has established that he could not have come into possession of this notebook prior to March 1, 1979, and thus he could not have made entries in it over the past four years.

Results of Investigation Concerning
Origin of Dr. Scafidi's Notebook

The cover of the notebook contains three printed lines, as follows:

7530-00-286-6952
FEDERAL SUPPLY SERVICE
* GPO. 1978-275-087

Inquiries conducted at the General Services Administration (GSA) disclosed the following information:

The first number on the cover is the stock number for this particular style notebook. GSA distributes this notebook to Federal agencies and periodically replenishes its supply by reordering copies from the Government Printing Office (GPO). Each time GSA reorders a supply of the notebooks from GPO, a separate contract number is assigned to the transaction and this number appears in the last printed line on the cover of the notebook.

In September 1978, GSA requisitioned from GPO 72,504 copies of this notebook under contract number 275-087, which number appears in line three on the cover of Dr. Scafidi's notebook. These 72,504 notebooks were delivered to seven GSA supply depots around the country between January 22 and February 14, 1979. Of these, 17,496 were delivered on January 22, 1979, to GSA's supply depot in Franconia, Virginia, the facility which supplies Federal agencies in the Washington, D.C. area, either in response to requisitions received directly from the agencies or through GSA's Self Service Stores.

GSA's supply depot in Franconia received no requisitions for this notebook from the Food and Drug Administration (FDA), located in the Parklawn Building, Rockville, Maryland. On February 11, 1979, GSA's Self Service Store #26, also located in the Parklawn Building, Rockville, requisitioned from the Franconia facility 720 copies of this notebook. This was the first such requisition made by this store in 1979. The 720 notebooks were delivered to the GSA store in the Parklawn Building on February 28, 1979, and were available for sale on March 1, 1979.

It is noted that FDA employees may purchase supplies directly from GSA's Self Service Store #26 or they may acquire supplies directly from the agency which is also supplied by the store. It is further noted that GSA's store in the Parklawn Building requisitioned and received additional shipments of 720 copies of this particular notebook in April, May, September, and November, 1979.

While Dr. Scafidi may have acquired his notebook anytime subsequent to March 1, 1979, he could not have come into possession of it prior to that date.

Mr. GORE. I might note after this second interview, Dr. Scafidi, we noted a GPO number on the front of your notebook [see p. 133] which indicated—it is in very small print—that it was manufactured in 1979 and could not have been available to you until at least March 1, 1979.

In preparation for your appearance here this morning you have evidently changed your story. You now insist that you have kept several small notebooks which were later transcribed in a process during which you regularly changed pens, colors of ink, and pencils because you are a nut about ink colors.

The reason this is important is that American consumers have spent over the last 18 months about $300 million unnecessarily, and about 20 percent of those consumers have experienced health reactions to the substitute product which is being sold because your actions led to the removal of the salt tablet solution.

As employees of the Food and Drug Administration responsible for this sequence of events, you are now testifying before a subcommittee of the Congress to justify the actions that you took. You have come here and told us a virtually unbelievable story.

Dr. Scafidi, I want to ask you one more time, and I want to remind you again of the laws against perjury, and I want to promise you that if this subcommittee determines, upon an examination of this transcript, that you have perjured yourself, it is not a matter that we will take lightly.

You have now been confronted with the sworn statements of three subcommittee investigators which directly contradict your earlier recollection of what you told them, and you have been confronted with a conflict between your two stories.

Let me ask you one more time, and I want you to reflect on it—did you sit down and make up this notebook in order to try and justify the decision that you took part in to remove these salt tablets from the market?

TESTIMONY OF MARY BRUCH AND DR. ARNAULD SCAFIDI—Resumed

Dr. SCAFIDI. I did not.

Mr. GORE. All right. The record will so stand.

You were asked about your relationship with this employee at Burton & Parsons. This is the company which makes the product which was then substituted for salt tablets. Why did an employee of Burton & Parsons make your hotel reservation in San Francisco?

Dr. SCAFIDI. I really didn't have a hotel reservation made. I came into town. I didn't have a room, so I just called Chet. I knew him. A lot of times these companies have blocks of rooms because they have a lot of people going, and sometimes I can get a room that way.

Mr. GORE. Have you other personal relationships with employees of Burton & Parsons?

Dr. SCAFIDI. Several of them are friends of mine. I have known them.

Mr. GORE. How many are personal friends of yours?

Dr. SCAFIDI. I don't know if I can take a count. I just never thought about it.

Mr. GORE. Think about it. A dozen?
Dr. SCAFIDI. Possibly.
Mr. GORE. Possibly as many as a dozen?
Dr. SCAFIDI. Possibly.
Mr. GORE. Have you spent any vacations with them?
Dr. SCAFIDI. No.
Mr. GORE. Have you had any business dealings with them?
Dr. SCAFIDI. Business dealings? In what sense?
Mr. GORE. In any sense.
Dr. SCAFIDI. I don't know of any business dealings. A couple of his kids are patients of mine in my private practice.
Mr. GORE. Of whose?
Dr. SCAFIDI. Mr. Laufer's.
Mr. GORE. Who is he?
Dr. SCAFIDI. Chet Laufer works for Burton & Parsons.
Mr. GORE. Does he pay you for treating his children?
Dr. SCAFIDI. He certainly does not. It always has been a practice not to charge a detail man or his family. I have never done that the whole time I was in private practice.
Mr. GORE. How many families of detail men or detail men do you treat in your private practice?
Dr. SCAFIDI. I don't know. I will have to go back through my files and look.
Mr. GORE. More than a dozen?
Dr. SCAFIDI. I don't know.
Mr. GORE. Less than a dozen?
Dr. SCAFIDI. I don't know.
Mr. GORE. One?
Dr. SCAFIDI. I know I treat one's family, two of his children.
Mr. GORE. The hotel where—the employee of Burton & Parsons, this company that benefited enormously from the decision that you and Mrs. Bruch caused, made your hotel reservation in San Francisco. You said the reason that took place was that you just breezed into town and you couldn't find a room and they would have a block of rooms. Is that right?
Dr. SCAFIDI. They usually have a block of rooms. I don't recall asking for a reservation in advance. I may have. I just don't recall.
Mr. GORE. Perhaps you are anticipating my next question, because you sent a check 5 weeks in advance for your hotel room.
Dr. SCAFIDI. For my hotel room or was it for courses I was going to take at the American Academy——
Mr. GORE. To register.
Dr. SCAFIDI. That was to register for courses in ophthalmology I was taking at the American Academy. If I recall right, it was $105.
Mr. GORE. So you knew and were actively thinking about your visit 5 weeks in advance.
Dr. SCAFIDI. I knew I was going.
Mr. GORE. And you neglected to make a hotel reservation?
Dr. SCAFIDI. It is so difficult. The way you make a hotel reservation at the academy is that you send the reservation request to the American Academy and they make the reservation for you. It is a very difficult thing.
Mr. GORE. Why did Burton & Parsons make the reservation for you then?

Dr. SCAFIDI. I blew into town from Newport. I knew I would be at Newport Beach for another meeting. I came up to San Francisco. I had neglected to make a reservation. I called Chet. He had an extra bed in his room, and I stayed with him.

Mr. GORE. You stayed in the hotel room with this employee of Burton & Parsons for the full week. Is that right?

Dr. SCAFIDI. However many days it was, I do not remember.

Mr. GORE. Mrs. Bruch, have employees of Burton & Parsons also made hotel reservations for you?

Mrs. BRUCH. Yes, they have.

Mr. GORE. On how many different occasions?

Mrs. BRUCH. Normally at the Academy of Ophthalmology I have asked that they do that.

Mr. GORE. How many times in Las Vegas?

Mrs. BRUCH. Probably two or three.

Mr. GORE. Three times in Las Vegas employees of Burton & Parsons made your hotel reservations?

Mrs. BRUCH. Yes.

Mr. GORE. Do you know a Mr. Thomas Manfuso?

Mrs. BRUCH. Yes, I do.

Mr. GORE. What is his position?

Mrs. BRUCH. President of Burton & Parsons.

Mr. GORE. Has he personally made reservations for you?

Mrs. BRUCH. I think that the sales manager, his brother, usually does it.

Mr. GORE. I have a hotel reservation that the subcommittee staff has copied from the Hotel St. Francis in San Francisco, Calif., dated November of 1979 for Mrs. Mary Bruch and Mr. Robert T. Manfuso, Burton & Parsons Co., Inc.

[Copies of hotel receipts follow:]

WESTERN INTERNATIONAL

Hotel St. Francis

UNION SQUARE • SAN FRANCISCO, CALIFORNIA 94119

CABLE STFRANCIS TELEX 278-34

MRS MARY BRUCH
C.R.ROBERT T.MANFUSO
BURTON PARSONS/CO INC
128 WESTHAMPTON A VENASHINGT

Cash and Paid

PRE-REG
11/10/79 5:51 ROOM NUMBER 3893

DATE	AMOUNT	REFERENCE	
11/09	581.00	RM GROUP	7 NIGHTS @ 83.00
	46.48	ROOMS TAX	
11/03	.50	LOCAL PHONE CALL	
TOTAL	627.98		

SIGNATURE Mary K. Bruch
ADDRESS 9501 Macarthur Blvd.
CITY Bethesda, Md. 20034

(14)

CLA / Boulder Trans Co. Bill #17

HOTEL SAHARA D 34264

NAME Mary Bruch, Ph.D
PLEASE PRINT

STREET FDA - Washington DC.
PLEASE PRINT

CITY AND STATE
PLEASE PRINT

Bruch, M

GUEST SIGNATURE

3519 ROOM	27.50 RATE	1 NO. OF GUESTS
1-15 DATE	1-16 DEPARTURE DATE	CLERK

1/13 1/16
WASHINGTON D C DHC/CH

D 34264

BURTON FIRSOLS

D 34264

MEMO		DATE	EXPLANATION	CHARGES	CREDITS	BAL DUE	PICKUP	ROOM NO
	1						• 27.56	NE3819.
	2						• 55.12	P = 19
	3							•#19 •
	4							
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PAID BY
AMERICAN EXPRESS

CL

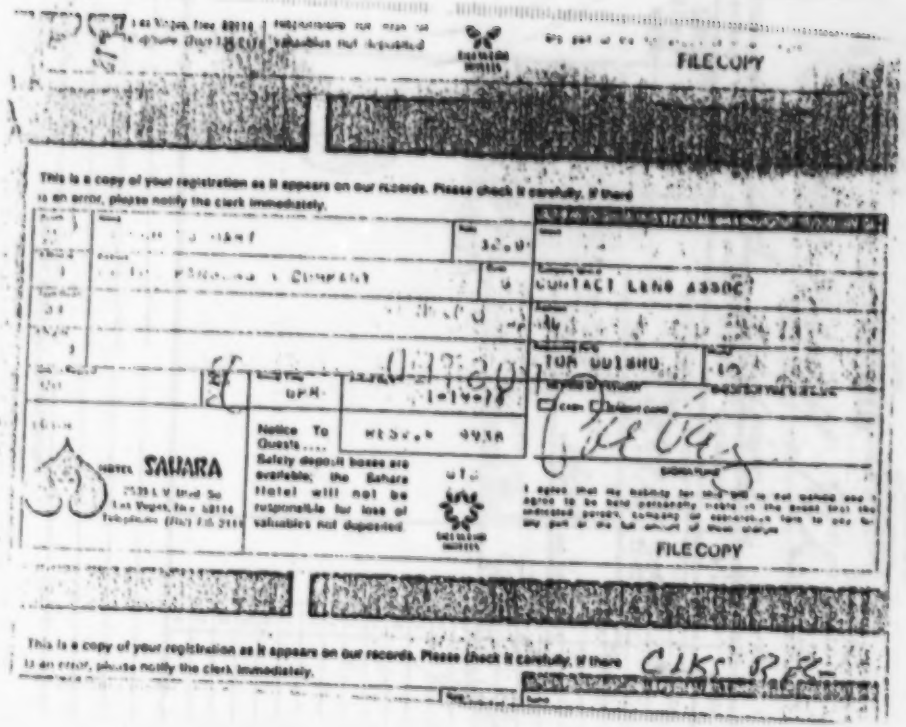
CHARGE TO

STREET

CITY - STATE

C C NO EXP DT

HOTEL SAHARA - LAS VEGAS, NEVADA



FILE COPY

This is a copy of your registration as it appears on our records. Please check it carefully. If there is an error, please notify the clerk immediately.

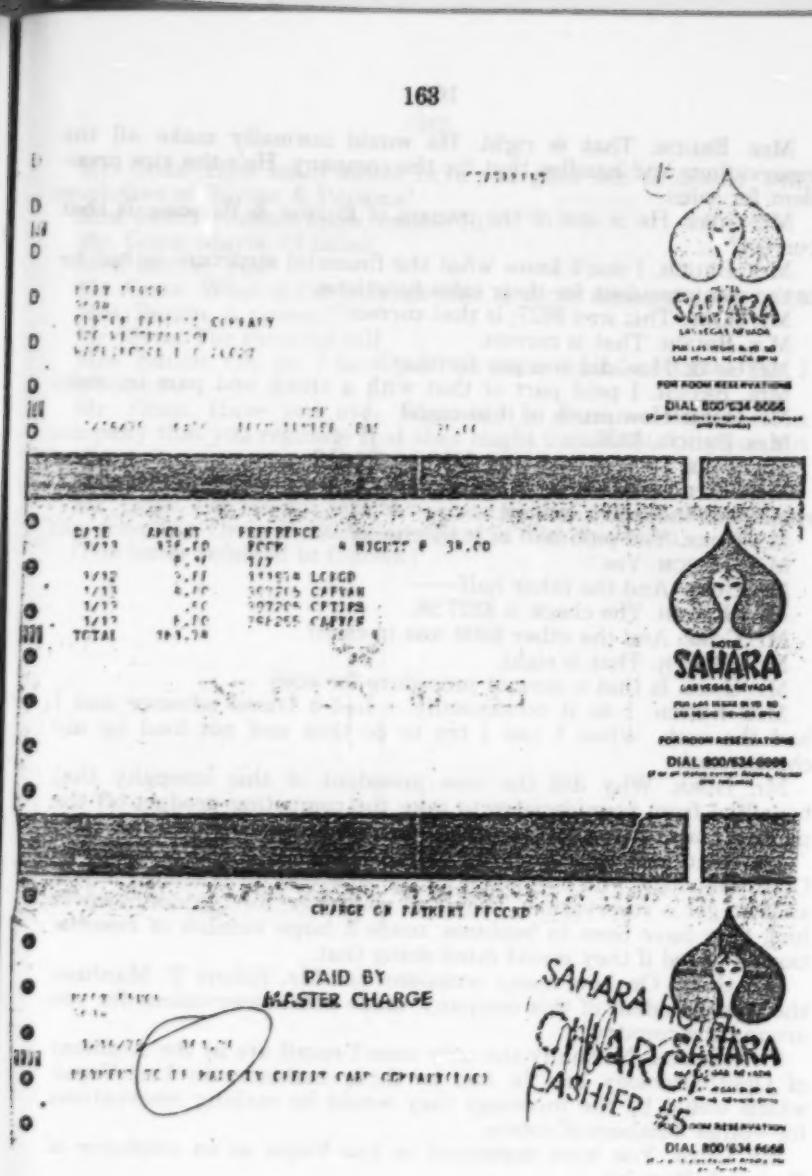
CONTACT LAND ASSOC

Notice To Guests.... Safety deposit boxes are available; the Sahara Hotel will not be responsible for loss of valuables not deposited

SAHARA

FILE COPY

This is a copy of your registration as it appears on our records. Please check it carefully. If there is an error, please notify the clerk immediately.



THE SAHARA
LAS VEGAS NEVADA

FOR ROOM RESERVATIONS
DIAL 800/634-6666

DATE	AMOUNT	REFERENCE	
9/29	139.00	POST	4 NIGHTS @ 39.00
	9.47	TAX	
9/30	5.00	3[illegible]8	LEISER
9/30	8.00	307215	CARVAN
9/30	.00	307205	CHIPS
9/30	8.00	296255	CARVER
TOTAL	169.47		

HOTEL
SAHARA
LAS VEGAS, NEVADA

FOR ROOM RESERVATIONS
DIAL 800/634-6666

CHARGE OR PAYMENT RECEIVED

PAID BY
MASTER CHARGE

SAHARA HOTEL
CHARGE
PASHIED #5

THE SAHARA
LAS VEGAS NEVADA

FOR ROOM RESERVATION
DIAL 800/634-6666

Mrs. BRUCH. That is right. He would normally make all the reservations and handles that for the company. He's the vice president for sales.

Mr. GORE. He is one of the owners of Burton & Parsons. Is that correct?

Mrs. BRUCH. I don't know what the financial structure is, but he is the vice president for their sales functions.

Mr. GORE. This was $627; is that correct?

Mrs. BRUCH. That is correct.

Mr. GORE. How did you pay for that?

Mrs. BRUCH. I paid part of that with a check and part in cash.

Mr. GORE. How much of it in cash?

Mrs. BRUCH. $300.

Mr. GORE. $300 in cash and $300 by check?

Mrs. BRUCH. I think the check is $327 or something. I don't remember the exact amount.

Mr. GORE. You paid half of it by check?

Mrs. BRUCH. Yes.

Mr. GORE. And the other half——

Mrs. BRUCH. The check is $327.98.

Mr. GORE. And the other $300 was in cash?

Mrs. BRUCH. That is right.

Mr. GORE. Is that a normal procedure for you?

Mrs. BRUCH. I do it occasionally. I had a travel advance and I had the cash. When I can I try to do that and not load up my charge card.

Mr. GORE. Why did the vice president of this company that benefited from your decision to take the competing product off the market make your hotel reservation in San Francisco?

Mrs. BRUCH. I had asked on that occasion. It is the Academy of Ophthalmology. I do not belong to the Academy. It is almost impossible to get a reservation. They had routinely, for I guess however long they have been in business, made a large number of reservations. I asked if they would mind doing that.

Mr. GORE. On how many occasions has Mr. Robert T. Manfuso, the vice president of this company, made hotel reservations for you around the country?

Mrs. BRUCH. Normally the only ones I recall are at the Academy of Ophthalmology and in two or three instances in Las Vegas, which would be the meetings they would be making reservations for—large numbers of rooms.

Mr. GORE. You were registered in Las Vegas as an employee of Burton & Parsons.

Mrs. BRUCH. I don't think so.

Mr. GORE. You are registered as Mary Bruch with Burton & Parsons; excuse me. Why were you registered Mary Bruch with Burton & Parsons?

Mrs. BRUCH. I assume because they made reservations for a number of rooms, and mine was one of those.

Mr. GORE. Is this standard practice for a company that benefits from FDA regulatory decisions to be making hotel reservations for the employees that make the decisions?

Mrs. BRUCH. I don't know if it is standard practice or not.

Mr. GORE. How many times have you gone out to dinner with employees of Burton & Parsons?

Mrs. BRUCH. I don't know, maybe 10.

Mr. GORE. Maybe 10 times.

Mrs. BRUCH. Yes.

Mr. GORE. What is the average cost of those dinners? Is it $100?

Mrs. BRUCH. A person?

Mr. GORE. For the total bill.

Mrs. BRUCH. Oh, no. I have paid on some occasions $25 to $30; I don't know.

Mr. GORE. Have you ever suggested to a representative of a company that you regulate that they might consider taking you out to dinner?

Mrs. BRUCH. Not to my knowledge.

Mr. GORE. Let me put into the record at this point a communication from Mr. Orrin B. Stine, president of Wesley-Jessen.

[The letter referred to follows:]

Wesley·Jessen

June 9, 1980

Ms. Susan Leal, Counsel
Sub-Committee on Oversight &
Investigations of the Committee
on Interstate and Foreign Commerce
2323 Rayburn House Office Building
Washington, D. C. 20515

Dear Ms. Leal:

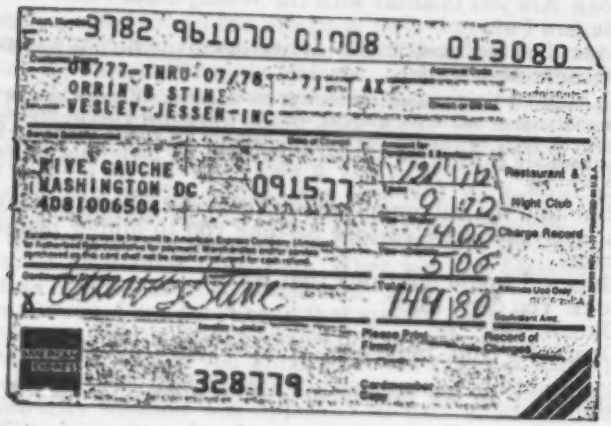
As you requested, I have located my copy of the American Express charge covering expenses for dinner and wine ($149.80) with Mrs. Bruch of FDA at Rive Gauche on 15 September 1977.

As required by IRS, the name of my guest and the principal subject discussed are given on the receipt. If the copies are inadequate, the original remains in my files.

Yours truly,

Orrin B. Stine
President

OBS/mlt
Enclosure


013080
07/77-THRU-07/78
ORRIN B STINE
VESLEY-JESSEN-INC
AX
RIVE GAUCHE
WASHINGTON DC
091577
Restaurant &
Night Club
Charge Record
Orrin B Stine
Please Print Firmly
Record of Charges
328779
Cardmember Copy

WASHINGTON DC
RIVE GAUCHE
ORRIN B STINE
080

Mr. GORE. Are you familiar with the Wesley-Jessen Co.?

Mrs. BRUCH. I am.

Mr. GORE. Let me read it into the record. It is a communication to the subcommittee staff.

As you requested, I have located my copy of the American Express charge covering expenses for dinner and wine, $149.80, with Mrs. Bruch of FDA at Rive Gauche on September 15, 1977. As required by IRS, the name of my guests and the principal subject discussed are given on the receipt. If the copies are inadequate, the original remains in my files.

Mr. Stine told the subcommittee staff that he offered to take you to lunch and you suggested that he take you to dinner instead. Is that correct?

Mrs. BRUCH. I would not think that is true.

Mr. GORE. You deny that?

Mrs. BRUCH. Yes.

Mr. GORE. Do you remember a $150 meal for two at Rive Gauche?

Mrs. BRUCH. I do not remember a $150 dinner for two at Rive Gauche.

Mr. GORE. Do you remember the dinner at Rive Gauche with Mr. Stine?

Mrs. BRUCH. I do not remember dinner at Rive Gauche with Mr. Stine. I think I testified that I think I had dinner with him at some point in the negotiations we were having at his insistence, and I mean insistence, that I sit down with him and discuss the studies that I had requested they do.

Mr. GORE. You two have cost consumers $200 million and you cannot justify your decision. Here you are running around at dinner, letting these people make your hotel reservations. This is not right. It is not right. I wish you were more forthcoming in your testimony. I promise you if you perjured yourselves we will pursue it because it is not right.

You have a particular closeness with Burton & Parsons, Mrs. Bruch. Would you say that you are more friendly than usual with the principals of the Burton & Parsons Co.?

Mrs. BRUCH. I don't know what you mean by more friendly than usual.

Mr. GORE. Let me put it this way: You have shared more meals with them; you have had more hotel reservations made by them than from representatives of other companies.

Mrs. BRUCH. I have had more hotel reservations made by them. I would not estimate that I have shared more meals with them necessarily.

Mr. GORE. In January 1977, the Bausch & Lomb research lab—let me review this briefly. Bausch & Lomb from 1971 until 1974 was the only company making soft contact lenses that were approved, and had the only disinfecting solution on the market.

Subsequent to that time, in 1974, the Burton & Parsons disinfecting solution came on the market. It cost 300 percent more. It came on the market in 1974.

If Burton & Parsons could find a way to get salt tablets off the market, then they stood to make a tremendous windfall.

In 1977, after the Burton & Parsons premixed formula was put on the market, and before the salt tablets were withdrawn from the market, Bausch & Lomb, the company which made the salt

tablets, reported to you the results of tests that they had performed on Burton & Parsons premixed solution, and they reported that the Burton & Parsons formula did not comply with the U.S.P. 19 interpretation of a preserved solution. According to FDA files, you prepared a memorandum dated May 10, 1977—it is already in the record and we will be glad to provide you with a copy of it so you can refresh your memory. [See p. 85.] According to FDA files you prepared this memo which was intended to refute Bausch & Lomb's accusations against the Burton-Parsons solution.

In that memo you describe for the FDA files the history of salt tablets as disastrous. Disastrous. What was the basis for your description of salt tablets as disastrous?

Mrs. BRUCH. I am not sure in that specific context.

Mr. GORE. That is what I am asking you about.

Mrs. BRUCH. Would you mind if we went back to something you said earlier? You said Burton-Parsons came onto the market. The boil-and-soak solution was approved as part of an application for the Hydrocurve lens. It was pursued not by Burton-Parsons but by the president of Hydrocurve who felt that salt tablets were a distinct risk to the public and wanted absolutely nothing to do with further use of salt tablets with the lens he was then——

Mr. GORE. The new formula was manufactured by Burton & Parsons. Is that correct?

Mrs. BRUCH. I don't know what you are referring to as the new formula.

Mr. GORE. 1971, FDA approves the first soft contact lens, Bausch & Lomb.

Mrs. BRUCH. With the salt tablets.

Mr. GORE. FDA approved not only the lens, but a complete system—lens, lens case, disinfectant, cleaner, and boiler.

Mrs. BRUCH. That is right.

Mr. GORE. You approved the whole system. From 1971 until 1974 there was only one such system approved and sold in the United States.

Mrs. BRUCH. That is correct.

Mr. GORE. That was the Bausch & Lomb lens plus disinfectant plus boiler.

Mrs. BRUCH. That is right.

Mr. GORE. In 1974 Hydrocurve, which is made by Continuous Curve, Inc.——

Mrs. BRUCH. That is correct.

Mr. GORE. It was approved as the second contact lens on the market. It chose to use a different cleaning system. Rather than using salt tablets it used a premix solution. For the first time, then, there was a second disinfecting solution on the market.

Mrs. BRUCH. That is correct.

Mr. GORE. That solution, which was part of the Hydrocurve system, was manufactured by Burton & Parsons. Is that correct?

Mrs. BRUCH. That is correct.

Mr. GORE. What was the basis for your description?

Mrs. BRUCH. Could you give me the page number?

Mr. GORE. Page 13. "Final tests, the alternatives are unpreserved saline which has been a disaster." What is the basis for your characterization of unpreserved saline as a disaster? You said on

May 10, 1977, that it had been a disaster. Why? What scientific data backs up that statement?

Mrs. BRUCH. I would like to read the memo. It has been a fair amount of time. I am really not sure of the context this is in.

Mr. GORE. It took $300 million of American consumers' money. What is the scientific basis for it?

Mrs. BRUCH. The very great risk that persons using it would develop corneal ulcers.

Mr. GORE. What do you have to back that up?

Mrs. BRUCH. It is a verified fact that the distilled water used by these patients contains pseudomonas, which is a very high risk to the eye.

Mr. GORE. Does boiling kill pseudomonas?

Mrs. BRUCH. Yes. But we know from the recorded instances of these infections, and we know from talking to patients and to ophthalmologists——

Mr. GORE. What recorded instances? As of May 10, 1977, name one recorded instance of a health problem of the kind you described associated with the salt tablets. Name one.

Mrs. BRUCH. What date?

Mr. GORE. May 10, 1977, on which date you described salt tablets as disastrous. Give us one health problem that substantiates that description.

Mrs. BRUCH. I was trying—many of the cases that have been reported to us have been after the fact of removing the salt tablets, and with some attendant publicity—please let me finish—and with attendant publicity that there is a risk. I have had optometrists and ophthalmologists stand up in meetings where I have delivered talks about our microbiological testing for these things, and ask me specifically if they could use preserved saline for their Bausch & Lomb patients because they did not like the deposits, did not like the discoloration, and felt this could be a risk to their patients.

I again would like to know more of the context from which you are asking the questions, but that is my concern. I am a microbiologist. I feel you do not hand the consumer under any circumstances a bottle where you might have a high level of pseudomonas. Granted you might feel we are making a judgment that is severe and is strict, but I think that you have to consider that this is strictly a cosmetic benefit that these patients are pursuing, that you cannot allow a risk of having these pseudomonas——

Mr. GORE. That is not what you said. You said on May 10, 1977, in this memo from FDA files which was in specific response to a challenge to Burton & Parsons' alternative, you said on May 10, 1977, that salt tablets had been disastrous.

Now, I have asked you to give me one case where a health problem of the kind you are talking about was caused by salt tablets as of May 10, 1977, and you are unable to do so.

Mrs. BRUCH. This review of the material is about the preservative effectiveness and about the microbiology. That is what I am referring to.

My reference to problems certainly is with what we have had numerous conversations and phone calls about from clinicians, with patients who do not prepare the saline, with doctors who tell their patients to prepare only once a week. This creates an in-

creased risk that they will have an infection. I felt this could not be justified. I assume that is my reference to "disaster," which I certainly would consider it.

Mr. GORE. It would cost $300 million. They have been on the market for 6 years. You described them as disastrous. You cannot cite one case. Instead, you say that when you have been at conventions, doctors leap up out of the audience and say, "Hey, there may be a problem with salt tablets."

Mrs. BRUCH. No, they did not say there was a problem.

Mr. GORE. Burton & Parsons?

Mrs. BRUCH. If they could use preserved saline.

Mr. GORE. It was a demand for Burton & Parsons product?

Mrs. BRUCH. It was the most common problem I got when I spoke to clinicians.

Mrs. GORE. You still cannct give us one single health problem?

Mrs. BRUCH. The clinical parts of these are not my responsibility. I am a microbiologist. That is the basis on which I make the argument for salt tablets.

Mr. GORE. You said it was disastrous.

Mrs. BRUCH. I think it is disastrous in the use of the salt tablets.

Mr. GORE. Mr. Lent, a few moments ago, went into Dr. Scafidi's memo dated in July 1976, which is just 6 months prior to your memo. You say you are not a doctor and you have to rely on him. He is the only ophthalmologist over there. His memo dated 6 months earlier says there is no problem. Why do you characterize the salt tablets as disastrous? What did you base that on?

Mrs. BRUCH. I think that in the use by the public and in the instructions given by many clinicians that it was disastrous. Certainly it was unacceptable.

Mr. GORE. In a letter dated December 9, 1977, from you to Louis Spizziri [see p. 114] you stated, in explaining the removal of salt tablets, that you "must deal with available objective facts and controlled studies rather than hearsay evidence."

What controlled studies? What controlled studies called for removal of salt tablets? What objective facts? Would it not be more accurate to describe your action as based on hearsay evidence, speculation, anecdotal information?

Mrs. BRUCH. May I see a copy of the letter?

Mr. GORE. It is already in the record. Staff will point it out for you.

Mrs. BRUCH. I am sorry. I didn't realize we had it.

Mr. GORE. That is all right.

Mrs. BRUCH. I have it.

I think I understand my comment. Very commonly we have many individuals write to us and say that in their practice of medicine, for whatever problem we are looking at, they have seen no difficulty.

Mr. GORE. All right.

Mrs. BRUCH. It is our standard approach that we do not rely on these anecdotal reports to us that they have not seen any problem in their practice. I think you would have to realize that the adverse reaction of corneal ulcers with identification of organisms will be a fairly rare event, and that the chances that these doctors might individually see it is not common.

Mr. GORE. How many millions of people were using the salt tablets as of this time in 1977? Was it a couple of million?

Mrs. BRUCH. I don't know. I have a fair idea now that it is about—it is very difficult. It depends on who you talk to, what numbers you get back.

Mr. GORE. Between 1 and 2 million up to that date. It is up to 4 million soft contact users now, but between 1 and 2 million as of that date. You cannot give us a single case.

Mrs. BRUCH. Of what?

Mr. GORE. Of a problem as of May 10, 1977.

Mrs. BRUCH. No; the first cases that I was aware of that confirmed what I had been very much afraid of were the pseudomonas in the bottles that the patients were using without any way I could see to remove it. This was the article by Krachmer. That was someone who asked——

Mr. GORE. We will get to that. We talked with the authors of that report.

Mrs. BRUCH [continuing]. Why we didn't push Bausch and Lomb before. I think at that point I had said a lot and written some things about what I thought was the risk. In my mind this was confirmatory. That is the first published information that I was aware of.

Mr. GORE. The authors of that study have told us that they did not confirm that any of those five cases were indeed related to the salt tablets. In any event, that took place after your decision to remove salt tablets from the marketplace.

Mrs. BRUCH. That article was quoted in the letter that we sent to the firm.

Mr. GORE. Your first insistence to Bausch & Lomb that the salt tablets be removed predated the study you are discussing now. Is that correct?

Mrs. BRUCH. That is correct. I had insisted for 3 or 4 years.

Mr. GORE. Why? The question is, what——

Mrs. BRUCH. I feel it is a risk to the public to use that product.

Mr. GORE. You said, and I quoted a moment ago from your letter to Mr. Spizziri, "You must deal with objective facts and controlled studies." What controlled studies were there? There was no controlled study, was there?

Mrs. BRUCH. We are talking about his reporting of infections and adverse reactions. I am talking to you about the microbiological contamination and what I considered to be a risk from that point of view, not from the——

Mr. GORE. Your own personal evaluation of a potential risk.

Mrs. BRUCH. Absolutely.

Mr. GORE. What studies were there? The fact is that there was no evidence on which you could have based your decision. You did it on your own feelings about the preference in the medical community for this alternative product which happened to be manufactured by this company, the representatives of whom were friends of yours.

Mrs. BRUCH. It is not correct that it is on the basis of preference. If I may go back to the studies I relied on in trying to make that decision.

Mr. GORE. When you first made your decision to compel the withdrawal of salt tablets from the marketplace, what studies did you rely on? Yes, please go back to that.

Mrs. BRUCH. I have served as a participant in a contract in the Bureau of Food in the Division of Cosmetics on the contamination of eye mascara. There are 14, I believe it is, and I would not want to be held to that exact number, but it is in that area. These were bona fide cases of corneal ulcers from contaminated mascara. The problems are somewhat similar. These mascaras continue to be preserved with thimerosal mercury preservatives. A number of these cases have been litigated in court. They are shown to be, and bona fide by culture, contaminated with pseudomonas and cause loss of vision and result in possible corneal transplants.

Mr. GORE. Mrs. Bruch, I don't want to interrupt you, but we are not talking about mascara.

Mrs. BRUCH. We are talking about products put around the eye rather than in the eye, more serious.

Mr. GORE. We are talking about a saline solution.

Mrs. BRUCH. The water is contaminated with pseudomonas which cannot be removed. Patients routinely use the solution for purposes they are not supposed to. When Bausch & Lomb was approved they never had a cleaner. The saline does not clean the lenses particularly well. Most lens wearers, after they take the lens out of the contact lens case, need further solution, pick up that bottle and use it. That is precisely where the risk is.

Mr. GORE. Should be used correctly.

Mrs. BRUCH. Of course.

Mr. GORE. It was not your experience that the mascara that you were earlier familiar with was commonly boiled before it was used?

Mrs. BRUCH. That is not even related.

Mr. GORE. Boiling kills pseudomonas.

Mrs. BRUCH. That is right, but we are talking about inviting abuse of the product which we know people did do.

Mr. GORE. Let me move on.

I would like to put into the record at this point a summary report of an inspection request dated September 22, 1977, also a December 12, 1977, memorandum from Mr. Kletch, and a December 12, 1979, memorandum from a Mr. Bryant of FDA. I also have a summary report of the 1977 inspection.

[Testimony resumes on p. 183.]

[The documents referred to follow:]

68-598 O—80——12

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PAAUTJAZ RUEVPCC 7712 2631900-UUUU--RUEVEMP.
ZNFB
FM DAVID H BRYANT CHIEF, MANUFACTURING REVIEW BRANCH HFD-322 DIV OF DRUG MANUFACTURING DHEW ROCKVILLE MD
TO BALTIMORE DISTRICT HFR-3250

SUBJ: INSPECTION REQUEST PENDING NDA 17-991 - TRI POL 43 CONTACT LENS

APPLICANT: G & S LENS COMPANY
KENSINGTON, MARYLAND

BULK MANUFACTURER: BURTON, PARSON & CO., INC.
SEAT PLEASANT AND EASTON, MARYLAND

FOLLOWING A RECENT (2/28/77) EVALUATION OF G & S LENS CO. IN WHICH WE ADVISED HFD-140 THAT THERE WERE GMP DEFICIENCEIS SUFFICIENT TO PREVENT APPROVAL OF THIS NDA, WE WERE VISITED BY MRS. MARY BRUCK WHO STATED THAT SHE HAD BEEN ASSURED BY REPRESENTATIVES OF THIS FIRM THAT ALL GMP DEFICIENCIES HAD BEEN CORRECTED. SHE REQUESTED THAT A

[illegible] TYC

NEW INSPECTION BE INITIATED TO VERIFY THIS. SHE EXPLAINED THAT FOR APPROVABLE LETTERS OR FIRMS SUCH AS THIS MUST ALSO BE SIGNED OFF BY THE BUREAU OF MEDICAL DEVICES. CONSEQUENTLY A GREAT DEAL OF ADMINISTRATIVE PAPERWORK IS INVOLVED. THIS SHE WOULD RATHER AVOID IF POSSIBLE.

YOU HAVE A COPY OF OUR 2/28/77 MEMO TO HFD-140 ADVISING THEM OF OUR REASONS FOR DETERMINING THAT G & S LENS CO. IS NOT IN COMPLIANCE WITH GMPS. PLEASE USE THIS DOCUMENT AS GUIDANCE IN CONDUCTING A RE-INSPECTION. PLEASE EXPEDITE SAID INSPECTION.

BUREAU CONTACT: WALTER S KLETCH HFD-322.

GR:322/AA
BT

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Baltimore District (HFR-3250)
Attn: Paula J. Oliver

December 12, 1977

FILE

Manufacturing Review Branch (HFD-322)
Division of Drug Manufacturing
Bureau of Drugs

AF 14-327

Inspection of G & S Lens Company, Kensington, Maryland dated October 11, 13, 17, 18, 1977

After review of the subject EIR including the firms response and additional NDA information we believe that all observations listed on the FD-483 issued to Mr. Michael J. Blaming following the subject inspection, except for observations number 7 and number 11 have been responded to adequately. We have consulted the NDE review team (medical-microbiological-chemical) and they have assured us that observations number 7 and number 11 will not present a hazard to the user of these lenses.

In regard to this firms compliance with CDMPR we believe that improvement has been made and that there is still room for additional improvement. However, we believe the deviations noted during this inspection do not warrant further regulatory action. We are recommending to HFD-140 that the application be approved.

Walter S. Kletch
Assistant to the Director
Division of Drug Manufacturing

cc: HFD-322 Firm File
HFD-320 R/F
HFA-224
WSKletch:rdj:12/12/77
wskletch 12/12/77

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE

1) Daily R/F 2) Ltr File

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Director, Division of Anti-Infective Drug Products (HFD-140)
Attn: H. Zell

DATE: December 12, 1977

FROM : Chief, Manufacturing Review Branch (HFD-322)
Division of Drug Manufacturing

SUBJECT: Approvable NDA 17-951, Tri Pol 43 Contact Lens

APPLICANT/MANUFACTURER: G & S Lens Company
Kensington, Maryland

SOLUTION MANUFACTURER: Burton Parsons and Company, Inc.
Seat Pleasant and Easton, Maryland

We have evaluated the operations of the firms listed above as they relate to compliance with Current Good Manufacturing Practice Regulations (21 CFR 211) and the referenced New Drug Application. We conclude that there is no reason to withhold approval of the referenced pending NDA insofar as it relates to these firms and the type of operations as specified in this pending new drug application.

Our evaluation is based in part on inspections conducted October 11, 13, 17, 18, 1977 at G & S Lens Company, July 21, 22, 1977 at the Easton facility of Burton Parsons and July 18-21, 1977 at the Seat Pleasant facility of Burton Parsons.

BACKGROUND INFORMATION

The initial inspection (2/16/77) revealed that the firm was non-operational. The second inspection July 26-28, 1977 disclosed various objectionable practices regarding the manufacturing and processing of the lenses. Management made some corrections during the inspection and submitted a detailed written response dated August 1, 1977 during a visit to the district office. The response indicated that generally all items had been corrected exclusive of those listed on FD-483 as items number 4 and 5 dealing with pyrogen testing. On September 16, 1977, Mrs. Mary Bruch telephoned Mr. Bernard T. Loftus and asked if he could expedite the re-inspection of G & S Lens Company in that she had been assured by representatives of Burton Parsons and Company that all GMP deficiencies had been corrected. On October 3, 1977 credentials were shown and a notice of inspection was issued to

Ms. Celia E. Greenberg, Director of Quality Control at G & S Lens Company. Ms. Greenberg declined to participate in the NDA inspection, requesting that the inspection be postponed until other responsible individuals returned from England. This current inspection was initiated on October 3rd, 1977 and completed on October 18, 1977.

In a letter dated March 23, 1977 from Mr. John Manfuso, Jr. of Burton Parson and Company, Inc. he states that by this date G & S Lens Company has manufactured three batches of lenses and is now ready for inspection. Considering the fact that the firm apparently manufactured lenses while they were not in compliance with CGMPR the Division might want to determine the disposition of these lenses and perhaps consider some additional testing to assure that these lenses possess the characteristics which they purport to possess.

David H. Bryant

David H. Bryant

cc: BLT-DO (HFR-3200)
HFV-234
HFD-322 Firm File
HFD-300 R/F
HFD-140 (NDA Orig)
WSKletch:rdj:12/12/77

Two previous inspections of this manufacturer of soft contact lenses have been made in response to requests from HFD-322 regarding pending NDA 17-951, TRI POL 43 Contact Lenses.

The initial inspection (2/16/77) revealed that the firm was non-operational. Related inspections at the Burton, Parsons and Co. plants in Seat Pleasant and Easton, Md. were also performed and revealed significant deviations from GMPR and NDA commitments. A recommendation of non-approval was made and the inspection was classified OAI.

The second inspection (7/26-28/77) was made in response to HFD-322 request dated 4/19/77. Various objectionable practices regarding the manufacturing and processing of the lenses were noted. These observations included the failure to test lenses for microbiological load prior to sterilization, the failure to perform any particulate matter testing in the clean room, the failure to have complete certification data for HEPA filters, inadequate batch production and control records, inadequate label control records, the use of an inadequate microbiological assay facility and inadequate component control records.

Management made some corrections during the inspection and submitted a detailed written response dated 8/1/77 during a visit to the district office on 8/4/77. The response indicated that generally all items had been corrected exclusive of those listed on FD-483 as Items #4 and #5, dealing with pyrogen testing of Buffered Normal Saline Solution. The firm stated that, Howard Zell, Bureau Drugs, Anti-Infective Division, had advised them that pyrogen testing was not a requirement for this type of product.

The inspection was classified as OAI and a recommendation of non-approval was made. Inspections of the Burton, Parsons & Co. plants were also made and were classified V.I.

On August 30, 1977, HFD-322 recommended to HFD-140 that NDA 17-951 was not approvable based on serious deviations from GMPR Regulations in the operations of this firm.

This current inspection was initiated in response to the HFD-322 inspection TWX dated 9/22/77. The assignment document detailed that Mrs. Mary Bruch, HFD-140 had been assured by representatives of Burton, Parsons and Co. that all GMPR deficiencies had been corrected. The inspection TWX requested verification of such corrections.

The inspection revealed several significant objectionable practices regarding the manufacturing/processing of the lenses as follows:

Paula J. Oliver

C & S LENS COMPANY
Kensington, Maryland 20795 10/11,13,17,18/77

ENDORSEMENT (Con't)

1. An inadequate procedure for handling rejected lots of plastic buttons.
2. The failure to have available chemical results for purified water used to rinse the incapsulation vials.
3. The failure to provide an accurate accountability/reconciliation of dry lenses in that the current method for completing batch records was not deemed to be adequate.
4. An adequate system for identifying roll labels.
5. The failure to date all raw data entered in laboratory notebooks and have such entries checked by a second individual.
6. The failure to adequately control and monitor the microbiological incubators, in that the 35°C incubator temperature had accidentally been reduced to 20°C on 10/11/77.
7. The failure to have written microbiological specifications for the buffered saline storage solution. Testing results available showed the presence of Pseudomonas aeruginosa or Pseudomonas spp.

Examination of records indicated that the time interval from hydration to autoclaving of the lenses did extend on occasions up to 10-11 days, during which time the lenses were stored in this solution.

8. Microbiological load data for encapsulated lenses under sterilization lot numbers 87752 thru 97774 revealed 20 of 24 plates incubated at 35°C were TBTC with Pseudomonas aeruginosa isolated. Results after 9/20/77, revealed that gram negative organisms appearing to be Pseudomonas spp. were isolated.

The firm revised some procedures during the inspection, and promised to make additional corrections. Specifically, the firm instituted corrections regarding those items listed as 1-2, 4-6 on the FD-483 prior to the conclusion of the inspection. Those items listed as 14-15 were noted as a result of the failure of NDA submissions to be promptly forwarded to the district files.

On 10/17/77, information regarding the firm's microbiological load data was presented to Dr. A. Casola and N. Zell (HFD-140); Paul Shette (HFO-120) and David Bryant (HFD-322). At this time, HFD-140 representatives indicated that they regarded the microbiological load data to be sufficiently serious to again withhold approval of the NDA.

C & S LENS COMPANY
Pensington, Maryland 10/11,12,17,18/77

ENFORCEMENT (Cont:t)

A written response (dated 10/26/77) to the inspection was addressed to the NLT-FO Compliance Branch Director and submitted by the Vice-President of Burton, Parsons and Co. during a visit to the NLT-DO office on 10/26/77. The response indicated that corrections had been made of some items. In response to other items, the firm took exception. With regard to Item #7, the firm feels that time intervals are not important and indicates that time intervals between hydration, encapsulation and autoclaving are not specified in the NDA. In regard to Items #11 and #13, the firm indicates that the NDA does not contain microbiological specifications for the hydration and encapsulating solution and further indicates that such specifications are not a requirement to the best of their knowledge.

F/U: Based on the deficiencies noted during the inspection, it is recommended that pending NDA 17-951 not be approved.

PJO/EHT/biw/10-28-77

Distribution:

a+enh: File
cc+enh: FFD-322
cc+enh: HFA-224
cc: NST-HP
cc: DFC
cc+profile update: P&B

FIR: C & S LENS COMPANY
Kensington, Maryland 20795 10/11,13,17,18/77 EWT

SUMMARY OF FINDINGS

This inspection was conducted at the request of HFD-322 regarding the pending NDA 17-951, Tri Pol 43 Soft Contact Lens, submitted by C & S Lens Company. The referenced assignment document indicates that CMP deficiencies found during the inspection of July 26-29 were sufficient to prevent the approval of this NDA. The assignment document requested an expedited inspection to verify the firm's contention that all CMP deficiencies had been corrected.

This inspection disclosed that the firm had made some corrections to those CMP deficiencies noted during the last inspection.

This inspection, however, uncovered additional CMP discrepancies, including:

1. The firm's procedure for handling lots of plastic buttons which were rejected by Quality Control for failure to meet acceptance criteria was released to production piecemeal for 100% inspection. The buttons were separated by production and those judged acceptable were used.

2. The chemical results for the purified water used to rinse the encapsulation vials were not available at the firm.

3. The system for identifying label rolls and providing for label accountability was inadequate, in that two rolls from different shipments could have the same numbers. Additionally, the firm was not aware that package inserts were to be handled as labeling.

4. The firm's current method of completing batch records was not adequate, in that the buttons listed as used in any particular manufacturing step (as identified by bag number and/or hydration lot number), may or may not have completed the processing and be present as the finished product as represented by the "batch records". Thus there is no batch accountability or reconciliation of the dry lenses.

5. Examination of the raw data contained in laboratory notebooks revealed that not all entries were dated regarding the setup date and reading date for microbiological entries. Record entries were not checked by second responsible and competent individual.

6. On 10/11/77 it was discovered that the temperature of the 35°C incubator had been accidentally reduced to approximately 20°C. The firm fails to adequately control and monitor the temperatures of the incubators used to hold the microbiological tests.

7. No microbiological specifications exist for the testing of the buffered saline solution for hydration and encapsulation (storage) of the soft contact lenses. Examination of those microbiological testing results available at the firm for review showed the presence of Pseudomonas aeruginosa or Pseudomonas species.

8. An examination of the last completed batch record revealed the length of time between the day of hydration through encapsulation to the date of autoclaving, (while the soft contact lense is in contact with the buffered saline solution) could be as long as ten to eleven days.

9. Microbiological load data for soft lenses (encapsulated) revealed that for test incubated at 35°C the organism count was too numerous to count in 20 of 24 plates for sterilization lot 87782 thru 97784. Lot 87782, the first sterilization lot for which microbiological data is available, isolated Pseudomonas aeruginosa; the remaining results were not isolated and identified. The microbiological testing procedure changed on 9/20/77. Colonies isolated for the first two sterilization lots were gram negative appearing to be Pseudomonas species. The remaining test results were not isolated and identified.

The firm revised some procedures during the inspection, and promised to make other corrections.

Mr. GORE. Did you visit a Burton & Parsons manufacturing facility in Baltimore on August 20, 1977?

Mrs. BRUCH. No, I did not.

Mr. GORE. Did you go to Seat Pleasant, Kensington, Md.?

Mrs. BRUCH. On what——

Mr. GORE. G. & S. Lens Co. in Kensington, Md.? Did you ever visit the G. & S. Lens Co. in Kensington, Md.?

Mrs. BRUCH. Yes, I walked through the facility to look at it.

Mr. GORE. That is a Burton & Parsons manufacturing facility; is that correct?

Mrs. BRUCH. I am really not sure of the contractual agreements. I know that those lenses use their solution. I think it is contractual or partially owned; I am not sure.

Mr. GORE. It is run by the Manfuso brothers. Is that correct?

Mrs. BRUCH. The lens company?

Mr. GORE. G. & S. Lens Co.

Mrs. BRUCH. I believe it is run by a man named George Mazaras.

Mr. GORE. Under contract to the Manfuso brothers?

Mrs. BRUCH. As I say, I am not sure what the stipulations are but I know there is an agreement of some kind.

Mr. GORE. They were having some problems out there. They are a contractor for Burton & Parsons. They are a bulk manufacturer for Burton & Parsons. They were having some problems.

This is a memo from David Bryant, Chief of the Manufacturing Review Branch with FDA. [See p. 174.] It states:

Following a recent evaluation"—by "recent" he says August 30, 1977—following a recent evaluation on August 30, 1977, of G. & S. Lens Co., in which we advised HFD-140 that there were good manufacturing practices deficiencies sufficient to prevent approval of this new drug application, we were visited by Mrs. Mary Bruch who stated that she had been assured by representatives of this firm that all good manufacturing practices deficiencies had been corrected. She requested that a new inspection be initiated to verify this. She explained that non-approvable letters on firms such as this must also be signed off by the Bureau of Medical Devices. Consequently, a great deal of administrative paperwork is involved. This she would rather avoid if possible.

Here the bulk contractor for the Manfuso brothers had a problem with an FDA inspector from the manufacturing review branch. You, from another branch, took it upon yourself to go out there personally——

Mrs. BRUCH. No, no. I never did that. I spoke to Mr. Bryant in our office.

Mr. GORE. You didn't go out to Kensington?

Mrs. BRUCH. Absolutely not.

Mr. GORE. You took it upon yourself to go visit the inspectors who were giving G. & S. problems.

Mrs. BRUCH. No.

Mr. GORE. And reassured them you had been advised that all the deficiencies had been taken care of. Is that right?

Mrs. BRUCH. That is not correct. Could I consult with my attorney?

Mr. GORE. Is this memorandum wrong?

Mrs. BRUCH. Could I consult with my attorney?

Mr. GORE. If it involves a matter of constitutional rights, surely. If it is a matter of fact or recollection of memory, then no.

Mrs. BRUCH. Mr. Gore, Dr. Gibson, my Division Director, has pursued straightening out these memos and the procedures involved in it. He has some of that information.

Mr. GORE. We will ask him about that, rest assured. He will be on the next panel.

Mrs. BRUCH. I do not have all of the details of that. However, it is not out of the ordinary to, in the process of trying to write your reviews and as far as any microbiological and sterilization problems involved in this, asked your opinion. That is what was involved in this. I would rather defer any of the answer to that because I think there is confusion.

Mr. GORE. We would rather you not defer if it is just as convenient. Who in Burton & Parsons assured you that all the deficiencies were corrected?

Mrs. BRUCH. I think Mr. Manfuso.

Mr. GORE. Mr. Manfuso assured you that all the deficiencies were corrected?

Mrs. BRUCH. Also probably Mr. Mazaras. I don't recall precisely. It was one or both.

Mr. GORE. What evidence did they present to you which formed the basis for your reassurance about their manufacturing deficiencies?

Mrs. BRUCH. They stated what the problem was and what they intended to do.

Mr. GORE. I see. So you were convinced that the problems that the manufacturing review branch had uncovered would be taken care of?

Mrs. BRUCH. The problems would have been from the field. They are sent into the manufacturing and review branch for their review before their recommendation comes to us.

Mr. GORE. This facility makes what are called buttons? It is the first step in the manufacture of the lens. Is that right? Is it something else?

Mrs. BRUCH. Burton & Parsons makes a polymer, tripol-43 is the polymer, a plastic. They put it into little molds and make buttons.

Mr. GORE. Yes.

Mrs. BRUCH. A lens manufacturer takes those buttons and makes a lens, grinds a lens and hydrates that lens so the water gets into it.

Mr. GORE. People put these in their eyes?

Mrs. BRUCH. They are first sterilized.

Mr. GORE. You got reports from the field there were manufacturing problems associated with them.

Mrs. BRUCH. Some had to do with microbiology.

Mr. GORE. And you were assured by your friend, Mr. Manfuso, that the problems would be taken care of.

Mrs. BRUCH. He explained to me what he intended to do.

Mr. GORE. You mentioned cutting down paperwork in the Bureau of Devices. Did the Commissioner or anyone else in FDA empower you to override or circumvent or alter the normal inspection and approval processes?

Mrs. BRUCH. No.

Mr. GORE. Did you receive permission from Mr. Gibson for this visit?

Mrs. BRUCH. I don't think so.

Mr. GORE. From Dr. Finkel?

Mrs. BRUCH. No.

Mr. GORE. From Dr. Crout?

Mrs. BRUCH. No, but this is not unusual procedure.

Mr. GORE. It is not unusual. Had you made any other such visit at any other time in behalf of Burson & Parsons or in behalf of any other company?

Mrs. BRUCH. Yes, I have.

Mr. GORE. How many times have you made such visits on behalf of Burton & Parsons?

Mrs. BRUCH. Burton & Parsons?

Mr. GORE. Yes.

Mrs. BRUCH. That is the only one I can recall. It is possible there was another one. Mostly these have to do with sterilization procedures.

Mr. GORE. All right. What we are talking about are visits to overturn an inspection. How many times have you done that? How many other times?

Mrs. BRUCH. I am sorry, there was no intent to overturn any inspection. It was to ask——

Mr. GORE. Certainly evidence idicates this was an effort to overturn inspection.

Mrs. BRUCH. It was to ask for an inspection to see whether they were rectified, I believe.

Mr. GORE. You stated that you had been assured that all of the deficiencies had been corrected, and you requested a new inspection to verify it.

Mrs. BRUCH. That is not the override. That is to ask in order to see what our agency and inspectors can verify that what I was told was true. That is all.

Mr. GORE. Is it not true that you also called on behalf of Burton & Parsons in September 1977.

Mrs. BRUCH. Called——

Mr. GORE. The Inspector's office.

Mrs. BRUCH. No, I did not.

Mr. GORE. We have a memo from the inspection office which indicates you did call.

Mrs. BRUCH. In the Baltimore district? Is that what you are referring to?

Mr. GORE. This is a memorandum which is already in the record. [See p. 176.] I would ask the staff to make sure it is pointed out clearly to the witness. It is from the chief of the manufacturing review branch to the Director of the Division of Anti-Infective Drug Products. Down near the bottom of that page, Mrs. Bruch, it states, "On September 16, 1977, Mrs. Mary Bruch telephoned Mr. Bernard T. Loftus and asked if he could expedite the reinspection of G. & S. Lens Co. in that she had been assured by representatives of Burton & Parsons Co. that all GMP deficiencies had been corrected."

Does that refresh your memory about the telephone call they said you made to the inspector?

Mr. GROVE. Did you ask her before in December 1977 whether they made the phone call? This refers to September. Maybe we misheard.

Mr. GORE. The question was this: Is it not true that you also called on behalf of Burton & Parsons in September 1977? Do you wish to change your response?

Mrs. BRUCH. No. Could I tell you my memory of this situation? That I either telephoned or went down to see Mr. Loftus, who was at that time Mr. Bryant's superior. I talked—I may have talked to Mr. Loftus on the phone and I am pretty sure I talked to Mr. Bryant in person about the problem because that is where Mr. Loftus sent me. He sent this telegram to the Baltimore district that you are reading from.

Mr. GORE. The inspection report found "serious deviations from good manufacturing practices." These included "failure to have available chemical results for purified water." "Failure to control microbiological incubator. Tests showed presence of pseudomonas."

This is the reinspection after you had given your assurance. This is the inspection report that occurred after you had given your assurances that everything had been taken care of. The Manfuso brothers had reassured you.

Therefore, they went back at your urging to have another inspection and found serious deviations from good manufacturing practices. This is in October 1977. "Tests showed presence of pseudomonas." Those sound like serious deficiencies, do they not?

Mrs. BRUCH. I am not sure what question you are asking me. The deficiencies that you specify——

Mr. GORE. Are serious?

Mrs. BRUCH. I would not consider them——

Mr. GORE. Presence of pseudomonas?

Mrs. BRUCH. Presence of pseudomonas was in the water prior to steam sterilization. I believe there was some concern this might be a problem.

Mr. GORE. So there is no problem if they are boiled?

Mrs. BRUCH. If they are not boiled——

Mr. GORE. It did not concern you they were there ahead of time?

Mrs. BRUCH. It is terminal sterilization and they will not be present.

Mr. GORE. We have included in the record a list of eight deficiencies that are described as serious deviations from good manufacturing practices.

Mrs. BRUCH. Could I say that Dr. Gibson has the details on all of the back-and-forth exchanges of this and he can explain it to you much more fully than I am able to.

Mr. GORE. Your testimony is that it is not unusual for you to act in this manner when there is an inspection by the manufacturing branch which shows serious deviations from good manufacturing practices, that it is not unusual for you on your own to call them up and say, "Don't worry about this. It will all be taken care of. Come over and expedite the approval."?

Mrs. BRUCH. That is not what I asked them to do.

Mr. GORE. I think the record will speak for itself. They said you asked them to expedite it.

Mrs. BRUCH. I asked them to expedite the reinspection to see whether the corrections had been made. It is not unusual for them to consult me about sterilization procedures. I have discussed other companies' sterilization procedures with them.

Mr. GORE. Do you know a Dr. A. Cassola and H. Zell of HFD140?
Mrs. BRUCH. Yes, they work in my division.
Mr. GORE. Page 2 states that the microbiological load data was sufficiently serious to again withhold approval of the NDA. [See summary, p. 179.]
Was the approval withheld?
Mr. GROVE. Is this the summary you speak of?
Mr. GORE. The staff will hand it to you. It is page 2 and then page 3. Page 2 is what I just read from. The answer to the question I just asked, I believe, will be obvious on page 3. It states, "Based on the deficiencies noted during the inspection it is recommended that the pending NDA not be approved."
Was the plant reinspected? Do you remember that?
Mrs. BRUCH. Honestly, as to these details, I don't have them.
Mr. GORE. The answer is yes. Following the inspection did you assure the drug manufacturing branch that the deficiencies in the plant will not present a hazard to the users of these lenses?
Mrs. BRUCH. The question was concerning the microbiological load in the water to wash the lenses. I answered that earlier. The firm met with the drug manufacturing branch and assured them that they were instituting the use of sterile saline which would obviate any microbiological problems which existed.
Mr. GORE. It was eventually approved, the record will show, but even after the approval the inspector said that deviations continued. "However, we believe the deviations noted during this inspection do not warrant further regulatory action."
Inspector Thomas said to our subcommittee staff that he had never run into a case where an NDA was approved without a final visit. Is it not fair to assume that Burton & Parsons, the principals of whom are friends of yours, received unusual attention from you during this approval process?
Mrs. BRUCH. I do not believe that.
Mr. GORE. And that the consumers of these products manufactured for and by Burton & Parsons ran an extra risk because of your desire to expedite the approval in spite of the repeated findings of deficiencies in their manufacturing practices.
Mrs. BRUCH. I do not feel there was a risk. Sterile saline was substituted. I cannot make any judgment that that was a risk.
Mr. GORE. Mrs. Bruch, we have more questions for you.
Dr. Scafidi, we have more questions for you, also.
I apologize to both of you and to the others present for the length of these proceedings, but we have a vote on the floor on the railway deregulation proposal. We will take a 20-minute recess. We will be back here at 12:30 to resume the hearings.
[Brief recess.]
Mr. GORE. The subcommittee will come back to order.
Dr. Scafidi, let me return to your notebook. You said that you compiled it in response to a contact by a lawyer in August 1979. Who was the lawyer who contacted you?
Dr. SCAFIDI. I don't remember whether it was August or September, but it was Manelli.
Mr. GORE. You are sure that it was Mr. Manelli?
Dr. SCAFIDI. I remember Mr. Manelli calling me. I don't know of any other lawyers that I talk to about this problem.

Mr. GORE. So in August or September 1979, Mr. Manelli called you and said he didn't know of any problems with salt tablets; therefore, on what did you base the agency's decision to remove salt tablets from the market? And in response to that telephone call you compiled your notebook from the reports in the smaller notebook.

Dr. SCAFIDI. About that time I was asked a lot of questions about salt tablets. I don't remember exactly when Mr. Manelli called me. I don't even remember whether it was later or earlier than that. The notebook was started, I guess. I can't put you in a chronological order because I really wasn't paying attention that close to all that.

Mr. GORE. Mr. Manelli has informed the subcommittee that he never contacted you prior to November 1979. There was a meeting in January 1980 at which he raised the questions which you now say were the provocation for your transcription back in August or September 1979. How do you explain that conflict?

Dr. SCAFIDI. I don't remember exactly when Mr. Manelli called me. I remember starting on the notebook. I don't know whether he precipitated it further or what. There are a lot of questions about salt tablets starting that summer and going on until now.

Mr. GORE. You furnished a copy of the notebook to Mr. Manelli in February 1980. Is that correct?

Dr. SCAFIDI. Sometime in there. He asked me for a copy and I gave it to him.

Mr. GORE. A moment ago you said that back in August 1979 or September 1979 he called you up and in response to that call you sat down and wrote the notebook, changing pens every few entries. However, he says that he did not contact you until much later. Then you gave him the notebook in February 1980. That appears to be a conflict.

Dr. SCAFIDI. I remember giving him the notebook later but I don't remember when he first called me. He asked me for the notebook.

Again, the notebook was just something for my own interest. I wasn't trying to make any big to-do out of it. I was collecting data——

Mr. GORE. You didn't want it to be a big to-do because it costs people $300 million. You did this on your own without any justification and you have evidently—well, I will let the record speak for itself.

Dr. SCAFIDI. If I may answer that a minute.

Mr. GORE. Sure.

Dr. SCAFIDI. I don't think that we have done something just voluntarily arbitrarily. In my professional judgment, after looking and talking to a lot of people in the last 5 years, and the fact that the problems that some patients are having with distilled water, I feel we made the proper judgment. I cannot be always involved, first with costs and then with health. My first responsibility is health. That's what I have to answer to, is health.

Mr. GORE. We talked this morning about the people who contacted you regarding problems with salt tablets. I asked you to name one doctor. You named a Dr. Lou Wilson.

Dr. SCAFIDI. Yes.

Mr. GORE. Dr. Lou Wilson gave his information publicly on February 11, 1980, to FDA in open session. I have a transcript of it right here.

Dr. SCAFIDI. That is correct.

Mr. GORE. Did he also call you up and muffle his voice on the telephone?

Dr. SCAFIDI. Dr. Wilson and I have been friends for quite a while. We discussed this problem and other ophthalmic problems before.

Mr. GORE. You see the implication of the question. You have 200-plus instances of alleged contacts with physicians, none of whom are named. I asked you for the name of one out of those 200, and you come up with one doctor who testified in open session. Can you give me one other doctor who contacted you?

Dr. SCAFIDI. I have talked to Dr. James Gordon about this problem before.

Mr. GORE. Where does he reside?

Dr. SCAFIDI. St. Louis.

Mr. GORE. Dr. James Gordon of St. Louis. Did he call you up on the telephone?

Dr. SCAFIDI. I speak to Dr. Gordon rather frequently.

Mr. GORE. Did he call you up on the telephone and give you instances of adverse reactions to salt tablets?

Dr. SCAFIDI. He possibly could have, or I could have——

Mr. GORE. Did he?

Dr. SCAFIDI. I don't remember exactly.

Mr. GORE. Give me one you are sure called you up and gave you an instance on the phone.

Dr. SCAFIDI. I try not to keep names because of the freedom question.

Mr. GORE. There is no privacy question in this congressional hearing.

Dr. SCAFIDI. I realize that, sir.

Mr. GORE. I am asking you for one name. You have a list of 200 instances and you cannot cite one name.

Dr. SCAFIDI. Mr. Chairman, I realize that this subcommittee has that privilege, but unfortunately we at the FDA, when we deal on everyday matters, do not have that privilege.

Mr. GORE. You are a Federal employee.

Dr. SCAFIDI. That is right.

Mr. GORE. Your actions have resulted in overcharges of $300 billion to U.S. consumers. I am asking you to justify that decision by providing the name of at least one doctor out of these 200 alleged adverse reactions that you report, and you cannot give me the name of a single one.

Dr. SCAFIDI. First of all, it was not a single decision based on just what I did.

Mr. GORE. Can you give me the name of a single doctor?

Dr. SCAFIDI. Dr. Gordon had a couple of cases.

Mr. GORE. Did Dr. Gordon call you up? Are you sure Dr. Gordon called you with a report of an adverse reaction?

Dr. SCAFIDI. Dr. Gordon and I speak rather frequently.

Mr. GORE. Did he call you with a report of an adverse reaction?

Dr. SCAFIDI. I do not remember.

Mr. GORE. Which entry might be that corresponding to Dr. Gordon's call?

Dr. SCAFIDI. I have no recollection.

Mr. GORE. Let me return to the question. Give me the name of one doctor who called you up with one of these 200 reported adverse reactions.

Dr. SCAFIDI. I don't remember.

Mr. GORE. You can't give me the name of one out of those 200?

Dr. SCAFIDI. No.

Mr. GORE. Let me remind you that your notebook contains 10 instances of adverse reactions reported since April of this year, since April 18, 1980, a little more than 2 months ago. Out of these 10 cases, half were pseudomonas. Surely you can remember the name of at least one doctor who in the last 2 months has told you about this dreaded infection that you report is associated with salt tablets.

Dr SCAFIDI. I don't remember any names.

Mr. GORE. You cannot give us the name of even one. Is that correct?

Dr. SCAFIDI. That is correct.

Mr. GORE. In the last 2 months, 10 doctors have called you up. In the last 2 months have any of them muffled their voices on the phone?

Dr. SCAFIDI. I don't remember.

Mr. GORE. You don't remember that, either. But you cannot cite a single one.

Is not the obvious conclusion that this notebook is simply fabricated?

Dr. SCAFIDI. No.

Mr. GORE. Back up and take it from another direction. I will put in the record at this point a memorandum of a meeting between Louis Whitmore, the president of Blairex Industries; Dan Manelli, the attorney you mentioned earlier; Peter Halberg, a doctor from New York; yourself; Victor Zafra, deputy director of the Bureau of Medical Devices, Daniel Brown, Ph. D.; Edward Kuntze; and Dan R. Beardsley, who are also with the Bureau of Medical Devices. The subject was salt tablets for use with soft contact lenses.

[The memorandum referred to follows:]

Blairex Laboratories
Indiannapolis, Indiana
AF 51-561
January 16, 1980

MEMORANDUM OF MEETING

Present: Louis Whitmore, President, Blairex Laboratories

Daniel J. Manelli, Attorney, Bushnell, Gage, Reizen & Byington, P.C., 1111 19th St., N.W., Washington, D.C.

Peter Halberg, M.D., New York, N.Y.

Arnauld Scafidi, Medical Officer, Bureau of Drugs

Victor Zafra, Deputy Director, BMD

Daniel Brown, Ph.D., HFK-460

Edward J. Kuntze, DCD, BMD

Dan R. Beardsley, DCD, BMD

Subject: Status of Salt Tablets for Use With Soft Contact Lenses

Since Mr. Manelli had requested the meeting he provided background information. He stated that he wished to get to the underlying issues involved in the agency's concern about the use of salt tablets with soft contact lenses and determine how Blairex can market the product. He indicated that he had sent an FOI request to the Agency on 11/29/79, for information on adverse effects of salt tablets and had not received any response to date. Also, as indicated in a previous meeting 11/27/79, he had received a printout from the National Registery of Drug - Induced Ocular Side Effects, in Portland, Oregon on soft contact lens solutions and had not found any adverse effects listed for the use of salt tablets as he had requested from the people handling that activity. In addition, he had made inquiry of Dr. Scafidi, ophthalmologist, separately, and searched the literature and found no reports of adverse reactions. In addition he was acquainted with the correspondence between FTC and FDA regarding FTC's concern about Bausch & Lomb anti-trust matters on limiting the use of accessories to be used with that company's soft contact lenses. He read from a letter that FDA's General Counsel had allegedly sent to FTC that FDA became concerned with the matters of bacterial corneal ulcers from use of salt tablets with soft contact lens users which appeared in the Archives of Ophthalmology, volume 96, January 1978, which was authored by Jay Krachmer, M.D., and John J. Purcell, Jr., M.D. He indicated from his review that this was

the only report that he knows about at the present time on adverse effects on use of salt tablets with soft contact lenses. Both he and Dr. Halbert emphasized that this article stated that it does not reach any conclusion that the infections of the five cases reported in that article was intended to connect the use of salt tablets with the cause of infections.

Mr. Manelli indicated in this meeting as he had in the 11/27/79 meeting that, in fact, you could obtain Eli Lilly's salt tablets from local pharmacists with directions for mixing with distilled water for use with soft contact lenses. In summary he indicated that with the millions of usages of salt tablets in this manner that the adverse effects had been minimal if not completely absent and that it was the position of he and the company that this product should be marketed.

Dr. Halbert, an ophthalmologist discussed his experience in the use of soft contact lenses. He stated that he and the corneal surgeons at St. Vincent's Hospital in New York City, with which he is associated, had never had a case of infections from the use of salt tablets. In fact he stated that he had checked with ophthalmologist in Las Vegas, Nevada; Houston, Texas; Lebanon, Indiana; Bellevue, Washington and Seattle, Washington and none of these individuals indicated that they had ever experienced infections which they associated with the use of salt tablets with soft contact lenses. Allegedly these physicians will fit from 150 to 180 lenses per year. Dr. Halbert had contacted the manager of Bausch & Lomb research clinics and other Bausch & Lomb officials and they were unable to furnish any adverse reports from the use of salt tablets with the Bausch & Lomb lenses. Dr. Scafidi commented that in his review of Bausch & Lomb's quarterly reports that came in on their NDA for their soft contact lenses that he had seen these adverse reactions involving infections. In his own practice as an ophthalmologist he may see two such corneal infections cases a week. Dr. Scafidi had discontinued the fitting of soft contact lenses in his practice as a result of the problems he has seen with these particular lenses. Infections he sees at the present time are patients who have been fitted by other practitioners.

Dr. Scafidi continued by saying that he did not understand why no adverse reports of the use of salt tablets had been furnished on the National Registry since he estimated that he himself had referred about 200 such cases to the registry. Some of these reports came from patients he had treated for corneal infection, others from reports coming to the Agency and still others from corneal surgeons and other practitioners who may call him up or may discuss the matter with him at various professional meetings. Apparently Dr. Scafidi and Mr. Manelli had talked to the same corneal expert and each of them came away with a different message from this individual. Dr. Scafidi reported that this expert was quite concerned about corneal infections from the use of salt tablets and Mr. Manelli indicated that this physician had no

best copy available

adverse reactions to report. Dr. Scafidi indicated that this discrepancy may result from practitioners not acknowledging the illegal use of salt tablets in their practices because of their concerns over malpractice suits.

Mr. Manelli indicated that there was an apparent discrepancy in the Agency's policy in regarding the products we are approving for use with soft contact lenses. He displayed a Bausch & Lomb enzymatic material which is intended for use as a disinfectant for soft contact lenses. Allegedly this is more difficult to handle by patients than salt tablets would be. In addition, he brought out the "Unisol" preservative free saline solution. He stated that it had been approved by FDA for use with soft contact lenses.

Dr. Scafidi indicated that in his review activities with FDA he had wrestled with the problem of providing directions for use for salt tablets to be used in solution with soft contact lenses and he was unable to come up with any. With regard to the Unisol product he indicated that this device is packaged sterile in a completely closed container and that it was the agency's position that it is a safer product than obtaining a vessel of distilled water from the pharmacist and using salt tablets at the discretion of a user. Dr. Scafidi indicated that he has had reported to him in the last three months 19 cases of infections that are salt tablet related.

There was a discussion with regard to the preservatives that are in salt solutions approved for use with lenses and the related allergic reactions. It was pointed out by Mr. Manelli that the report he received from the National Registry for Drug-Induced Ocular Side Effects had a large number of these types of reports for various of these preservative containing products. From that standpoint it appears to the company that the salt tablets are safer than the preserved materials.

Mr. Manelli asked if any other firms besides Blairex had received regulatory letters. Mr. Beardsley indicated no, however, investigations are underway in these matters.

The representatives of the company indicated that the economics of salt tablets should be allowed to be marketed. They pointed out that the Unisol product at about forty cents per container would run a patient approximately $140.00 per year. Dr. Scafidi and Mr. Link indicated that the questions regarding safety would over-ride economics in this regard.

A discussion was held as to what actions the company may take now. They indicated that they were not really prepared to submit an NDA at this time and FDA representatives indicated that it might not be

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an appropriate time to submit such an application unless the company was prepared to undertake a large clinical study. It was indicated that there would be an ophthalmology classification panel meeting on February 11 and 12, 1980 and that Mr. Manelli, if interested, might try to schedule an appearance with a Dr. Talbot of FDA. Mr. Manelli indicated that they would consider that matter.

Finally, Mr. Manelli indicated that he was not encouraging that other firms receive regulatory letters, however, FDA's regulatory pressure on only one firm appears to place them at a competitive disadvantage with other companies.

He also requested that we check out his previous FOI request. Both Mr. Manelli and Dr. Scafidi were going to check with the Drug-Induced Ocular Side Effect Registry again for reported salt solution adverse reactions.

Dan R. Beardsley

cc:
HFR-9240 (Zenk
DET-DO, HFR-5440
HFK-1
HFK-2
HFK-460(D.Brown)
HFD-140 (A. Scafidi)
HFK-114 (Kuntze)
HFK-110 (PC)
HFA-224
DBeardsley:jp:1/22/80
Initial:DBeardsley:1/24/80
r/d:jp:1/29/80
Initial:DBeardsley:1/30/80
t/f:jp:1/30/80

Mr. GORE. There are three sources of reports cited in this memorandum. I am now reading from the bottom of page 2, Dr. Scafidi:

"Some of these reports came from patients he had treated for corneal infection, others from reports coming to the agency, and still others from corneal surgeons and other practitioners who may call him up or may discuss the matter with him at various professional meetings."

Why didn't you mention that in your testimony?

Dr. SCAFIDI. What is there to mention?

Mr. GORE. You never mentioned reports from your own practice of corneal infection related to salt tablets.

Dr. SCAFIDI. I never thought it was that necessary to mention it. All reports had problems.

Mr. GORE. Have you in fact had cases that you have treated for problems related to salt tablets?

Dr. SCAFIDI. Yes, sir, I have.

Mr. GORE. Refer to your notebook, if you would, and identify by the numbers recorded to the left of the adverse reaction entries which of those are your patients.

Dr. SCAFIDI. I have no idea. I don't keep a number of who is who.

Mr. GORE. Would you be willing to provide that to the subcommittee?

Dr. SCAFIDI. The number?

Mr. GORE. Let me ask you this: Give me the names of any patients that have experienced corneal infection as a result of using——

Mr. EARNEST. Point of order, Mr. Chairman.

Mr. GORE. The attorney will please be seated.

Mr. EARNEST. May I identify myself for the record?

Mr. GORE. Yes. You may.

Mr. EARNEST. I am Broughton Earnest, counsel for Dr. Scafidi.

Mr. GORE. That will suffice. You may be seated and you may advise your client on a matter of constitutional right if you wish.

Mr. EARNEST. Thank you, Mr. Chairman.

Mr. GORE. Not as to matters of fact.

Dr. SCAFIDI. I think information concerning my private practice is privileged to those patients involved and I do not think I can give you names without their permission.

Mr. GORE. The subcommittee will accept that response. Would you be willing to give us the adverse reaction reports in your own practice with the names of the patients you allegedly treated deleted?

Dr. SCAFIDI. If I can take the time out to go through my files I will try to find them for you. I have three file drawers full of charts.

Mr. GORE. Do you recall specific cases?

Dr. SCAFIDI. I never saw a corneal ulcer in my own personal practice.

Mr. GORE. I thought you did.

Dr. SCAFIDI. Keratitis. That is a corneal inflammation.

Mr. GORE. You told them you treated corneal infection caused by salt tablets.

Dr. SCAFIDI. That is a keratitis. That is the same thing. A corneal infection of the cornea is a keratitis, inflammation of the cornea.

Mr. GORE. What about pseudomonas?

Dr. SCAFIDI. In private practice I have currently seen pseudomonas, also.

Mr. GORE. You are unable to identify in your notebook those entries which correspond to your own patients?

Dr. SCAFIDI. I am not.

Mr. GORE. What are the numbers at the left?

Dr. SCAFIDI. Sequential order, just to keep a number of how many are in the book, simply that.

Mr. GORE. What is the date of the first entry?

Dr. SCAFIDI. It is not on here. I don't recall.

Mr. GORE. But it does go back 4 years?

Dr. SCAFIDI. In the little notebook, the original ones. I don't know if I took them in the same order that I collected in the little tiny notebooks. I had them in a drawer. I use up a notebook, throw it in the trash, maybe go to lunch, maybe answer a phone call, go to a meeting, come back, and when I had a spare moment pick up the next notebook.

Mr. GORE. You transcribed it into the large notebook because of the attorney's call. I guess that was because you anticipated some possible problem that might lead you to transcribe the evidence. Why would that not also lead you to save the original notebook?

Dr. SCAFIDI. I don't think I anticipated a problem. I anticipated somebody saying to me they had never seen a case of adverse reaction due to a salt tablet.

Mr. GORE. Are you aware, Dr. Scafidi, that the draft report on the results of the survey prepared by Dr. Charles Gressle, of the Bureau of Medical Devices, stated, "The cleaning products most frequently mentioned are the Preflex, Flexol, and Normal cleaning solutions manufacturerd by Burton and Parsons as having the most frequent adverse reaction."?

Dr. SCAFIDI. I don't recall ever seeing such a report.

Mr. GORE. Are you aware of the health problems experienced by 20 percent of those who use the substitute products that are on the market because of your decision, Mrs. Bruch?

Mrs. BRUCH. I think using 20 percent is very high. My estimate would be around 10. I will give you two or three if you want.

Mr. GORE. I have had estimates of between 20 and 30.

Mrs. BRUCH. I also have had people say it was 50, but as far as trying to get some kind of rational objective information, somewhere around 10. If you want to say 12 even, OK. That is where I would put it.

Yes, I am very much aware. Thimerosal is a known sensitizer. Dermatologists have a national, North American, and international dermatitis group. They have estimated incidence of thimerosal allergy that is about 3 to 4 percent in that population who visit dermatologists' offices. The incidence in the population at large is probably about 1 or 2 percent at the very highest.

What you are referring to frequently is an irritation reaction. The mucous of the eye is very difficult to show sensitization reaction. From what I have learned in this situation, the most likely reaction is that some of this is idiosyncratic. The patient simply cannot tolerate the preservative and we are really not sure why. It is not likely an irritation reaction.

Mr. GORE. Again that is contrary——

Mrs. BRUCH. If you would put the irritation reaction which will o away when the patient stops using this against the corneal ulcer vhich can cause blindness and necessity for a corneal transplant, here is really no comparison.

Mr. GORE. The existence of which was never indicated prior to our decision.

Mrs. BRUCH. But the potential certainly is there if you have a consumer handle a bottle with pseudomonas in it every day.

Mr. GORE. In your mind. Let me ask you about medical evidence n the thimerosal. I personally believe it is ironic that the substiute product sold after you got the salt tablets taken off the market id produce a health reaction up to 20 percent—there is some ispute about the percentage—in those who use it now. The Palo lto Medical Clinic wrote the Director of the Bureau of Medical evices and describes the reaction to thimerosal as an extreme eaction:

These symptoms I am discussing are severe ones. All of the following chemicals ave this preservative: Boil-and-Soak, Flexol, and Normal. We have tried using Boil-nd-Soak in heat sterilization on Bausch and Lomb new saline to cut down on the mount of thimerosal but this has not or will not work. The symptoms always recur.

Thimerosal is a mercury compound. Is that correct?

Mrs. BRUCH. Yes.

Mr. GORE. If a consumer happens to be allergic to thimerosal, oes he have to throw away the contact lenses after they have once een soaked in thimerosal?

Mrs. BRUCH. There is something called a rescue operation for enses that have some——

Mr. GORE. To purge the lenses?

Mrs. BRUCH. Yes.

Mr. GORE. How much does that cost?

Mrs. BRUCH. All that involves is simply running your lenses hrough several times with unpreserved saline.

Mr. GORE. That may work.

Mrs. BRUCH. I understand certain patients have done this and een successful.

Mr. GORE. Others have had to throw away their lenses?

Mrs. BRUCH. I would imagine that is possible.

Mr. GORE. Then they have to shell out another $250 to $300.

Mrs. BRUCH. That is not correct. Replacement lenses don't cost hat.

Mr. GORE. How much do they normally cost?

Mrs. BRUCH. Prices of lenses have been going down consistently. Ve have now a $10 lens. Somewhere between $10 and $20.

Mr. GORE. That is exclusive of the doctor's visits, the treatment.

Mrs. BRUCH. Replacement lens are not that big a deal.

Mr. GORE. This Palo Alto clinic says. "In the 2 years I have vorked here"—the person writing from the Palo Alto clinic——

Mrs. BRUCH. Who signed the letter?

Mr. GORE. Sandra Schoof. "In the 2 years I have worked here nd the large amounts of people we see on a clinical basis there as never been a problem with the salt tablets and people making p their own saline solution."

[The letter referred to follows:]

M Talbot DEVICES - MEDICAL
JAN 18 1979
2 - 6
JAN 16 1979

PALO ALTO MEDICAL CLINIC
300 HOMER AVENUE, PALO ALTO, CALIFORNIA 94301 • (415) 321-4121

FA:DGC

9 January 1979

David Link
Director of Bureau of Medical Devices
Food Drug Administration
8757 Georgia Avenue, Silver Springs, Maryland 20910

Dear Mr. Link:

I am writing this letter in accordance with the FDA's recent law which bans salt tablets from the market for the use of contact lens cleaning.

I am an optometrist assistant at the Palo Alto Medical Clinic and have worked in this field for two years now. Thousands of people are prescribed soft contacts every year by our two resident doctors of Optometry here at the Clinic. Each of those patients that are given soft contact lenses also are given a Care Kit by us for the maintenance and care of their lenses. The patient reads his cleaning instructions over carefully and then returns for a return appointment which at the time, the Care Kit is discussed again by patient and instructor. At this point, the patient has a clear understanding of the use, maintenance and care of their lenses.

Many people have been given cold chemical care kits for proper cleansing and septisizing of their lenses. In each of these chemical products there exists a preservative Thimerasol in varying percentages. The chemical cleansing kits are given by our doctors to the patient, 90% more than the heat sterilization, namely because of its quick and easy use. The problem that we have encountered over this past year since more and more of our patients have been using cold chemical aseptisizing is the extreme reaction to the Thimerasol preservative. We are most certain that the reactions of burning and redness has been pinpointed to Thimerasol. When we encounter a patient with this type of a reaction, we have the patient purge their lenses of chemicals for three days and then switch them to heat aseptising in which they make up their own saline solution daily. Their saline solution is made with the Bausch & Lomb salt tablets now banned from the market and since it is made daily by the patient, there is no need of a preservative. Once these patients are taken off of these chemicals with Thimerasol in them, and begin using the heat sterilizer making their own saline solution, their symptoms of reaction disappear immediately within a few days. These symptoms I am discussing are severe ones. The patient almost always has severe burning and extreme redness. They are unable to wear the lenses that have absorbed the chemical. When he lays off them for a few days he becomes asymptomatic. As soon as the patient resumes wear and regular cleaning techniques with the chemicals, the symptoms of redness and burning return within a few days. All of the following chemicals have this preservative... Boil and Soak, Preflex, Flamel and Normal. We have tried using Boil and Soak in heat sterilization or Bausch & Lomb's new saline to cut down in the amount of the Thimerasol a patient uses, but this has not or will not work. The symptoms always recur.

Our main purpose of prescribing to the patient the Bausch & Lomb salt tablets in distilled water is to relieve them of these severe reactions. Our success has been 100% in making the patient asymptomatic, by removing his use of chemicals to the making of his own solution with the salt tablets.

The problem at hand is a grave one in which there seems to be no alternative to turn to if the patient has a reaction, since all that exists on the market at this time are chemicals with this preservative.
Another question at hand, concerns the existing people who have had chemical reactions and are now using salt tablets. What alternative do we have for this patient? Not only have these people been subject to putting out a great sum of money for contact lenses, but they have encountered these problems of reactions and they feel their doctors should foresee. We now have no choice, but to discontinue the use of the patient's contact lenses and refund their money to them, if they should have a reaction to the existing chemicals.
One of the questions you may ask is how clean can making up your own saline solution be? In the two years I have worked here and the large amounts of people we see on a clinic basis, there has never been a problem with the salt tablets and people making up their own saline solution.

We certainly hope that the FDA will retract this law or at least place the product on the market that is acceptable to the FDA without any preservatives in this product.

Thank you very much for your consideration.

Sincerely,

Sandra Schnof
Dr. Waldron's nurse
Palo Alto Medical Clinic
Contact Lens Dept.

SS:pm

Mr. GORE. How many letters in the record at the FDA are there like that? Lots and lots and lots, aren't there?

Mrs. BRUCH. Letters we have received have been primarily emphasizing the increased costs and a number have written, and there are not many, many. There are some.

Mr. GORE. Hundreds and hundreds?

Mrs. BRUCH. Not specifying that they can't tolerate the thimerosal, no.

Mr. GORE. There are hundreds and hundreds of letters protesting removal of the salt tablets; is that right?

Mrs. BRUCH. I can only speak for the letters I have received myself which I would say would be somewhere between 100 and 200 letters, if that many, but I would give a generous estimate. The majority of those, I state again, are concerned about the increased costs. Some of them mention they do not tolerate the preservative.

Mr. GORE. Dr. Scafidi, you said a moment ago you were not aware of this draft report on the Gressle survey. [See p. 37.] Are you not the Project Officer on that?

Dr. SCAFIDI. I don't know who he is.

Mr. GORE. Bureau of Medical Devices.

Dr. SCAFIDI. I am Project Officer on the Drug-Induced Ocular Side Effects contracts. We had 1 year in which the contract had a rider on it which the Bureau of Devices collected data.

At that time Mr. Chet Reynolds was handling it and the report went to him.

Mr. GORE. This is the report in the Bureau of Medical Devices on the survey for which you were Project Officer.

Dr. SCAFIDI. I am sorry; I don't recall seeing such a report. Mr. Chet Reynolds was handling the rider under my contract and all the device things went to him.

Mr. GORE. This is the one which shows 20 percent complaints on preservatives.

Refer to your large notebook again, Dr. Scafidi. I don't find those instances of adverse reaction which came directly to the agency.

Dr. SCAFIDI. I have no way of telling which one is who.

Mr. GORE. Where are they in the agency? Where are they filed in FDA? You said in this memorandum of January 16, 1980—and you have that there; this is the one where Dan Manelli and the other folks I mentioned were present [see p. 191]—you said there were three categories of reports of adverse reactions to salt tablets. One category is your own patients. Another category is reports coming directly to the agency. Third, you have the reports from doctors who called you up.

I am asking you about the second category, reports coming into the agency directly. Where in FDA are those filed? We would like to see that file.

Dr. SCAFIDI. I don't have that file.

Mr. GORE. Does that file exist?

Dr. SCAFIDI. It is right here. When they called me at the agency, that is the report of the agency. I just wrote it in my little notebook.

Mr. GORE. You have what is called a drug experience network, right, a sort of registry of adverse reactions kept in the agency?

Dr. SCAFIDI. Yes.

Mr. GORE. Where is that filed?

Dr. SCAFIDI. That is in the Division of Drug Experience.

Mr. GORE. Then these reports were filed in that file; is that right?

Dr. SCAFIDI. I don't know that I sent them up there.

Mr. GORE. Why not?

Dr. SCAFIDI. I never really thought about it. Contact lens stuff, when I was handling it, came to me, so I took care of it.

Mr. GORE. This is really embarrassing, you two. Seriously, this is really embarrassing. This is just a big rigamarole. You have come in here with this absolutely fantastic and unbelieveable story. You go through every single detail of it. Wherever you look you find an outrageous inconsistency or conflict.

Why don't you just tell it like it is? I know that is not going to be possible. Evidently you have just decided, the two of you, to tough it out, as they say, but it is really embarrassing, isn't it? It is kind of ridiculous to string it out and prolong it, but everywhere you look and examine the veracity of your statements you find an outrageous inconsistency. Does that not give it earmarks of something that has just been fabricated out of thin air?

Mr. GROVE. Is that a question directed to Mrs. Bruch?

Mr. GORE. I will direct it first to Dr. Scafidi and then direct it to Mrs. Bruch without further interruptions from counsel.

Dr. Scafidi?

Dr. SCAFIDI. As far as I know I am telling it like it is.

Mr. GORE. Mrs. Bruch?

Mrs. BRUCH. Is the question—I am not sure what you are asking. If I fabricated something, I certainly am not. My only concern was the welfare of the consumer who would be exposed to the potential risk of serious eye infection and potential loss of the eye based on very good microbiological data.

Mr. GORE. We have a copy of the file that I was asking about, Dr. Scafidi, to which reports like the ones which came to you are normally referred. It does not contain any such reports, so evidently you did not refer these alleged reports to that file.

I will not prolong this further. We have literally dozens of other lines of questioning that point out apparent inconsistencies in the story you are giving the subcommittee today. I have warned both of you in advance of the implications of perjury. The subcommittee, upon review of this document, if it uncovers any evidence of a violation, I assure you, will take it quite seriously because as an oversight subcommittee we rely heavily on candor on the part of Federal employees in pursuing our mandate to try to see that the laws function properly and that those in regulatory agencies perform up to the best of their ability in the pursuit of their mandates.

You are both excused at this point.

Let me call the last panel with my apologies for the long delay.

Dr. Richard Crout, Director of the Bureau of Drugs; Dr. Merle L. Gibson, Director of the Division of Anti-Infective Drug Products.

Gentlemen, if you would both stand, raise your right hands and be sworn.

Do you swear to tell the truth, the whole truth, and nothing but the truth, so help you God?

Dr. CROUT. I do.

Dr. GIBSON. I do.

Mr. GORE. If you would both formally identify yourselves to the reporter. You are accompanied by——

Ms. SISK. Joanne Sisk.

Mr. GORE. You will not be offering testimony?

Ms. SISK. That is right.

Mr. GORE. You do not need to be sworn.

Dr. Crout, if you would identify yourself, and Dr. Gibson, and then, Dr. Crout, proceed with your statement.

TESTIMONY OF DR. J. RICHARD CROUT, DIRECTOR, BUREAU OF DRUGS, FOOD AND DRUG ADMINISTRATION, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH AND HUMAN SERVICES, AND DR. MERLE L. GIBSON, DIRECTOR, DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS, FDA, ACCOMPANIED BY JOANNE SISK, ASSOCIATE GENERAL COUNSEL FOR ENFORCEMENT, OFFICE OF THE GENERAL COUNSEL, HHS

Dr. CROUT. I am Dr. J. Richard Crout, Director of the Bureau of Drugs. On my right is Dr. Merle Gibson, Director of the Division of Anti-Infective Drug Products in our Bureau.

On my left is Ms. Joanne Sisk from the Office of our General Counsel.

I am here today at the subcommittee's invitation to discuss FDA's regulation of soft contact lenses, particularly the sale solutions used in their disinfection.

Soft—hydrophilic—lenses are made of water-absorbing plastic. They are brittle when dry, but soft and pliable when saturated with water. When placed in the eye, they conform to the shape of the cornea and, for most people, are more comfortable than hard contact lenses.

Soft lenses are marketed and approved by the Food and Drug Administration—FDA—as entire systems. The system includes the lenses, the containers they are stored in, a heater for boiling them, and the solutions necessary for their cleaning and boiling.

Soft contact lenses were first developed in the mid-1960's. Because of concern that proper clinical trials be done to assess the safety and efficacy of these lenses, and further concern that proper disinfection systems be developed to minimize the risk of eye infections, the FDA announced in 1968 that soft contact lenses would be regulated as new drugs and that approved new drug applications would be required prior to marketing.

The first NDA submitted to us was by Bausch & Lomb in April of 1969. The firm submitted a new drug application in October 1969 and resubmitted it in July 1970 after a series of FDA guidelines for the study of soft lenses had been developed. This application was approved on March 18, 1971, and the Bausch & Lomb lens became the first approved soft contact lens in this country. Approved with the lens was a heater disinfection system to be used daily, a cleansing solution, and a solution container for the consumer to use in making the necessary salt solution from a 250 mg. tablet of sodium chloride.

An effective disinfection system for soft contact lenses was considered by FDA to be essential then, and continues to be so consid-

ered. The absorbed water in these lenses provides a potential site for the growth of bacteria. Serious eye infections, while very uncommon, have been reported in users of soft lens and are usually due to poor hygiene.

In April 1974, the Hydrocurve lens, made by Continuous Curve, Inc., became the second approved soft lens for general use. This lens was approved with a preserved pre-mixed salt solution because the manufacturer did not want to pursue the use of a consumer-prepared salt solution for heat disinfection. Since that time, the FDA has approved for use with soft lenses only premixed salt solutions containing preservatives against bacterial growth or prepackaged sterile unit-dose solutions.

The reasons that FDA has not approved nonpreserved, multidose solution of the type prepared from 250 mg. sodium chloride tablets are as follows:

Such systems leave a nonsterile residual in the mixing bottle used for daily preparation of the isotonic solution.

The consumer may use this solution as a wetting agent for the lens and, thereby, instill unboiled solution directly into the eye.

Improperly diluted solutions may be too concentrated or too diluted, with resultant damage to the soft lens or irritation of the user's eye.

Improper storage of the distilled water used in preparing these solutions can result in further contamination with bacteria.

In subsequent years, a variety of new lens and disinfection systems have been approved so that the marketplace today contains over 30 brands of soft lenses and both heat and chemical disinfection systems. Since the passage of the medical device amendments to the Federal Food, Drug, and Cosmetic Act, the regulation of these products has been handled by the Bureau of Medical Devices in consultation with staff in the Bureau of Drugs. Soft lenses have also been discussed on several occasions before the Medical Device Panel concerned with ophthalmological products.

On May 22, 1978, Mr. David Link, then Director of the Bureau of Medical Devices, sent a letter to Bausch & Lomb requesting withdrawal of its salt tablets from the marketplace. The reason for our safety concern was that salt tablets may pose a greater risk than premixed solutions for the reasons I have cited above. This position was taken as basically a prudent attempt to minimize risk, to prevent trouble. It was not taken on the basis of solid evidence of a comparative risk between salt tablets and premixed solutions.

I might also point out that the position was well-known to our advisory committee. I will also point out that the notebook used by Dr. Scafidi was his personal one. The data in that were not considered as part of this decision and have played no role in the data used for decisionmaking purposes.

Mr. GORE. It was submitted officially to the registry, was it not?

Dr. CROUT. I guess it was.

Mr. GORE. It was. Of the 201 instances on the registry, 196 of them came from Dr. Scafidi's notebook.

Dr. CROUT. I am just pointing out that the decision to favor premixed preserved salt solutions by comparison with salt tablets was simply taken on the basis of what was considered a prudent approach.

Mr. GORE. You are talking now about the approval of the premix and not the withdrawal of the salt tablets.

Dr. CROUT. Even at that time this was not an issue in which there were comparative data available to support that decision on the basis of data.

On November 1, 1978, Bausch & Lomb stopped its marketing of these tablets. This has proven to be a controversial action because the premixed solutions in the marketplace are more expensive than the formerly available salt tablets.

In addition, the preservative in the premixed solution is irritating to the eyes in certain patients. The latter problem has been solved by the approval in 1979 of several brands of unit-dose sterile solutions that contain no preservatives, but a number of consumers complain about the high cost of these solutions by comparison with the former salt tablets.

The possible reintroduction of salt tablets has been discussed extensively by the Ophthalmic Device Section Panel on Feburary 11, 1980, and on June 2, 1980. The panel has advised the Bureau of Medical Devices that it believes salt tablets can be reintroduced to the marketplace providing certain precautions are taken. These precautions include a smaller unit size of the tablet so that only 15 ml. of solution can be prepared at one time, and special warnings in the labeling for the consumer. I am advised that the Bureau of Medical Devices agrees with this recommendation in principle.

In sum, it appears that salt tablets may return to the market under conditions that should obviate some of our past concerns.

Let me turn to a different subject; namely the employees involved in the review of soft lenses.

For several weeks, the staff of the Subcommittee on Oversight and Investigations has been conducting an investigation of the travel records and personal conduct of the two Bureau of Drugs employees most involved in the review of the applications for soft lenses, Dr. Arnauld Scafidi and Mrs. Mary Bruch. Both employees are under subpena to appear at this hearing.

Last week I was informed of the findings of your staff and on that basis have requested an investigation by the policy management staff of FDA. When the investigation is complete and the two employees have had the opportunity to present their views, I will take whatever action is appropriate. While matters of this type arise most uncommonly, they have happened before, and this is our usual approach in handling them.

Because of the public attention brought to Dr. Scafidi and Ms. Bruch by this hearing, I feel obliged to put the allegations about them in perspective. Because of their personal contacts with friends in certain drug firms, particularly at professional meetings, they may have created an appearance of too close a relationship with industry. Whether they have violated the Department's standards of conduct regulations is not determined at this time. I am aware of no evidence of favoritism to any drug firms in the handling of applications. The positions they have taken on various scientific issues related to soft lenses are well known within FDA and throughout industry.

The reputation in the Bureau of Drugs of both Dr. Scafidi and Ms. Bruch is that they are consumer-oriented, conservative in their

safety judgments, highly knowledgeable and competent, hard working, not easily swayed from their convictions, and honest. Dr. Scafidi is, by election of his peers, president of the medical officers association in the Bureau of Drugs. I, along with many colleagues in the Bureau, would be deeply shocked if their investigation turns up any evidence of favoritism in handling applications or other serious impropriety.

I recently reviewed our practices for informing employees about the Department's standards of conduct regulations and agency policy on relations with industry.

All employees are given a copy of the standards of conduct regulation at the time of their initial employment. On March 29, 1979, former Commissioner Kennedy also issued to all FDA employees a memorandum entitled "Our Dealings With Regulated Industry and With One Another," detailing both procedures and attitudes appropriate for FDA employees in their dealings with industry representatives. Commissioner Goyan will soon issue another memorandum to all agency employees on this topic.

The mere issuance of regulations and memoranda does not assure, however, that they are read and understood. Dr. Goyan has asked each Bureau Director to communicate agency policies to our professional staffs. I am, therefore, planning a personal presentation on the standards of conduct to the Bureau of Drugs as part of our regular seminar program for all professional employees.

FDA employees take great pride in the integrity with which they handle the difficult problem of meeting regularly with industry representatives and yet maintaining the professional distance appropriate for regulatory officials. I am confident our staff is sensitive to, and supportive of, agency policy on standards of conduct.

I would be pleased to answer any questions you may have.

Mr. GORE. Thank you, Doctor.

Dr. Gibson, you do not have a statement?

Dr. GIBSON. No, I do not have a statement.

Mr. GORE. You state serious eye infections related to soft lenses are very uncommon. How uncommon are they? Can you qualify that?

Dr. CROUT. I don't think it is possible to tell. The reports that are in the medical literature, in the papers that I think you are familiar with, are the Krachmer paper and one by Bohigian. There is a paper about to be published by Forster. The first one reports 5 cases of corneal ulcers in soft lens users, the second one 24 cases. Many of these were with pseudomonas. The third one reports 238 patients with ulcers and 33 percent of these are in association with soft lenses.

Therefore, I think it is unquestioned that corneal ulcers appear——

Mr. GORE. None of the cases decided have identified salt tablets as the cause?

Dr. CROUT. Some used salt tablets and some used the solution.

Mr. GORE. None identified salt tablets as the cause.

Dr. CROUT. No, it is not possible.

Mr. GORE. Can you cite a single case where salt tablets properly used have caused eye infection?

Dr. CROUT. Well, there is no question that a number of these cases used salt tablets. A number of them also used the solutions. What you cannot tell——

Mr. GORE. There is no indication that in any of these cases proper use of salt tablets has caused any problem?

Dr. CROUT. I don't know that one can say that.

Mr. GORE. Would it surprise you to hear that at the time FDA pressured the manufacturer of salt tablets to withdraw them from the marketplace that there was no evidence whatsoever on which to base that decision?

Dr. CROUT. It would not surprise me. I know that. I knew it then.

Mr. GORE. Why did you approve that action?

Dr. CROUT. As I mentioned, I didn't approve it. This was handled by the Bureau of Medical Devices. I would have handled it the same way had it come to me.

Mr. GORE. On the basis of no evidence?

Dr. CROUT. This is a prudent determination of what looks like a reasonable system for disinfecting lenses. The system with salt tablets, at least the one that the Bausch & Lomb system has, allowed the preparation of more solution than was necessary. The solution can become contaminated. One can dip fingers in it.

Mr. GORE. One can dip fingers in the preserved solution, can one not?

Dr. CROUT. Yes, but it has a preservative in it to kill the bacteria.

Mr. GORE. Excuse me. The preservative is a bacterial static, is it not?

Dr. CROUT. Yes.

Mr. GORE. It does not kill bacteria, does it?

Dr. CROUT. No.

Mr. GORE. One can dip one's fingers in it and the bacteria would be there. Is that right?

Dr. CROUT. I will have to seek a microgiologist's opinion on that.

Mr. GORE. I think we have one in the room.

Mrs. BRUCH. Do you want me to answer?

Mr. GORE. No, that is all right. No, we don't want your statement. Thank you, anyway.

Let me restate the question. If you can't get advice from any other source—it is my understanding that the preservative in the formula is a bacterial static, that it prevents the multiplication of the bacteria, and that improper use of the premixed formula can cause problems just as improper use of the salt tablets can cause a problem.

You stated, No. 1, that serious eye infections with soft lenses of all kinds are very uncommon. You further state that they are usually due to poor hygiene.

You would agree, would you not, that poor hygiene associated with soft contact lenses can lead to infections regardless of the kind of solutions used?

Dr. CROUT. Yes.

Mr. GORE. By the same token, would you not agree that if salt tablets are used as directed there is no greater risk involved?

Dr. CROUT. That is impossible to say. I don't think one can assert that one way or the other.

Mr. GORE. The FDA has implicitly asserted that and the expense to the consumers has been $300 million. It seems to me you ought to be able to back it up.

Dr. CROUT. This is one of those tough decisions where you have two different options in front of you. Sometimes those decisions are made by experts making a reasonable attempt to decide which one carries the lowest risk. I think this decision was made in that way at this time.

Mr. GORE. You did a risk analysis?

Dr. CROUT. We don't do a formal risk analysis.

Mr. GORE. Did you do any kind of risk analysis?

Dr. CROUT. No.

Mr. GORE. No risk analysis? Did you do an analysis of the safety of putting mercury in the eye every day for a period of years.

Dr. CROUT. No.

Mr. GORE. That is the choice that you left consumers with. You said you cannot have these salt tablets anymore because these two FDA employees have this theory there may be a problem with it. We don't have any evidence of a problem, but they say there may be one. Instead, then, we want you to put mercury in your eye every day.

Dr. CROUT. Mercury has been used in the eye for a long period of time.

Mr. GORE. What is known about the safety of thimerosal?

Dr. CROUT. I cannot give you data on this. I am not prepared on that. It is a well-established preservative for use in the eye and in the concentrations we approve it now.

Mr. GORE. Do you have any analysis of the safety of using thimerosal on a regular basis in the eye?

Dr. CROUT. It has been used for years in eye solutions. I think we made the assumption——

Mr. GORE. So have salt tablets.

Dr. CROUT. I am——

Mr. GORE. You ruled one out and ruled one in. Why?

Dr. CROUT. I am simply saying—I will get out my testimony and reread it.

Mr. GORE. I don't want you to do that.

Dr. CROUT. You may disagree with the decision. All I am doing is saying that this was a decision made by the institution, not by two people. It was known to the advisory committee, concurred in by the Bureau Director of Medical Devices. The reasons are clear. You may agree with them or disagree with them.

Mr. GORE. Let me ask you about a statement on page 3 of your testimony where you say that on May 15, 1978, David Link, then Director of the Bureau of Medical Devices, sent a letter to Bausch & Lomb requesting withdrawal of its salt tablets from the marketplace.

I would like to read from a typical letter in FDA files, one of dozens of such letters, sent by FDA in response to complaints from consumers and ophthalmologists and optometrists protesting removal of salt tablets from the market. I quote from FDA's letter:

Quite candidly, the withdrawal of salt tablets which coincided with the distribution of Bausch & Lomb's preserved saline came unexpectedly to the FDA.

That letter is from David Link, the same David Link who wrote the letter to Bausch & Lomb requesting withdrawal of the salt tablets. How do you reconcile the first letter requesting the removal, the one you cite in your testimony, with the letter that the same individual wrote to consumers saying that this decision came unexpectedly to the FDA?

Dr. CROUT. I don't. You would have to ask Mr. Link.

Mr. GORE. It seems to me it is part of an effort by FDA to take heat off itself for an unpopular decision made with no scientific justification and in so doing shift the blame to the industry. Is that a fair conclusion?

Dr. CROUT. I have no comment on that.

Mr. GORE. Do you know who drafted the letter written by David Link to Bausch & Lomb requesting the withdrawal of salt tablets from the marketplace?

Dr. CROUT. I am told Mary Bruch did.

Mr. GORE. Mary Bruch drafted that letter. Then David Link writes to a consumer saying it was a surprise to him.

When were you first aware of Dr. Scafidi's notebook?

Dr. CROUT. In the course of this investigation going on, not more than 2 or 3 weeks ago.

Mr. GORE. Would the staff provide Dr. Crout with the notebook? I would like you to examine it, Dr. Crout. Would you consider the entries in this notebook as scientifically admissible data?

Dr. CROUT. No; I have seen a Xerox of this before and asked myself that question. The answer is "No."

Mr. GORE. You see how the entries are in different colored ink?

Dr. CROUT. I wasn't thinking of that. I was just thinking that these entries without being dated and without knowing what solutions were being used with them, and without a lot of other information, without verification, do not constitute a scientific study. Also, I don't know that anybody thought they did. I don't know that Dr. Scafidi alleged it was a scientific study.

Mr. GORE. He is project officer of this survey and registry which has been compiled with $75,000 of public money. He submitted the reports in that notebook to that survey, 201 of the alleged instances of adverse reactions to salt tablets. Out of the 201, 196 came from that notebook. Would that cause you to question the validity of the information in the survey?

Dr. CROUT. I think if we queried that survey or that registry the information would be reported back to us in the form of case report forms and—I am not sure about the side information. I am not sure how this would be reported back to us.

Mr. GORE. Let me tell you the kind of effect.

Dr. CROUT. Let me finish, please.

Mr. GORE. Give your answer first.

Dr. CROUT. The only thing that counts in a registry of that kind is individual cases entered on individual case report forms, so to the extent that anything in the notebook was not so entered it is not scientifically useful.

Mr. GORE. Nevertheless, it is used. The FDA has given its imprimatur on it. They trust the officials at FDA. As evidence of that trust and the kind of impact it can have I have an article from the American Academy of Ophthalmology. This is dated February

1980, Volume 87, No. 2. This is the official Journal of the American Academy of Ophthalmology. The title of this article is "Interim Report: National Registry of Possible Drug-Induced Ocular Side Effects," by Frederick T. Fraunfelder, M.D.

A recent survey by the Registry has uncovered 201 cases of corneal infections seen in patients using the salt tablet technique for contact lens sterilization. All cases were seen by ophthalmologists. Cultures were primarily staphylococcus aureus but included 10 cases of Pseudomonas aeruginosa, 7 cases of streptococcus, and 6 cases of fungal ulcers. Although one of the major manufacturers has removed this type of product from the market, others are still commercially available. It is the opinion of some that the product, although sound, suffered because there was no preservative.

This goes out to ophthalmologists all over the country from this notebook.

[The article referred to follows:]

65-328 O—80—15

(From the Journal of the American Academy of Ophthalmology, February 1980)

Interim Report: National Registry of Possible Drug-induced Ocular Side Effects

FREDERICK T. FRAUNFELDER, MD

In the past two decades, public, medical, and governmental interests have created increased emphasis on examining possible adverse effects of drugs. Ophthalmic effects have been prominent in the three recent major drug disasters, ie, thalidomide, indochlorohydroxyquin, and practolol. Medicolegal implications from adverse drug effects are equally important, since they are probably the cause of approximately 20% of malpractice cases. The clinician must be aware that the package insert is the legal standard by which one is judged as to accepted methods of administration, dosages, and indications for therapy. To vary from this standard may place a significant legal burden on the prescriber.

The National Registry of Drug-Induced Ocular Side Effects is the first attempt of any specialty group to do post-marketing surveillance as a flagging system of possible adverse drug-related events. This type system seems to be the direction the FDA is encouraging in part due to the apparent success of this Registry. This report will review only a few adverse drug-related events in the Registry reported by ophthalmologists, obtained from the literature, the FDA, and drug companies, or supplied by foreign general medical drug registries.

From the Department of Ophthalmology, University of Oregon Health Science Center, Portland, Oregon.

Presented at the Eighty-Fourth Annual Meeting of the American Academy of Ophthalmology, San Francisco, November 5–9, 1979.

Supported in part by the Research to Prevent Blindness.

Reprint requests to F. T. Fraunfelder, MD, Department of Ophthalmology, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201.

TIMOLOL MALEATE (Timoptic®)

Over 550 case reports of adverse responses, both ocular and systemic effects, to this drug have been reported by ophthalmologists to this Registry within the past 11 months. While most reports were of limited significance, others may significantly influence how and to whom this drug should be prescribed. The data per se in the Registry will be presented elsewhere.[1]

While local ocular effects do occur from this drug, the more significant adverse effects are the same systemic side effects seen with any beta-receptor blocking agent.[2] This includes:

CNS: depression, anxiety, confusion, dysarthria, and hallucinations;
Cardiovascular: bradycardia, arrhythmias, heart failure, and possible myocardial infarcts;
Pulmonary: dyspnea, airway obstruction, bronchial spasm and pulmonary failure;
Dermal: maculopapular rash, alopecia, and hives;
Gastrointestinal: diarrhea, nausea, and cramping.

STERILIZATION OF CONTACT LENS

A recent survey by the Registry has uncovered 201 cases of corneal infections

seen in patients using the salt tablet technique for contact lens sterilization. All cases were seen by ophthalmologists. Cultures were primarily *Staphylococcus aureus* but included ten cases of *Pseudomonas aeruginosa*, seven cases of streptococcus, and six cases of fungal ulcers. Although one of the major manufacturers has removed this type of product from the market, others are still commercially available. It is the opinion of some that the product, although sound, suffered because there was no preservative. However, there have been numerous cases reported to the Registry of ocular irritation secondary to sensitization or allergic reactions to thimerosal which is a preservative in some soft contact lens soaking solutions.

NEOMYCIN

As expected with such a commonly prescribed antibiotic, numerous allergic reactions have been reported to the Registry following topical ophthalmic use of neomycin. However, new data of interest to our specialty are becoming available in the dermatologic literature. The incidence of contact dermatitis due to topical application of neomycin is between 1 and 6%, depending on the surveys.[3] If neomycin has been used topically for longer than seven days on inflammatory dermatosis, the incidence of allergic reaction is increased thirteen-fold over matched controls. Neomycin preparations for minor infections rarely should be used over seven days. In addition, the physician should be aware that if the patient has been previously exposed to neomycin or is currently on this therapy for over seven days, there is a significantly higher chance of an allergic response. That this can be transposed to ocular disorders is conjectural, although drug representatives have so stated.

IBUPROFEN (Motrin®)

This is one of the largest selling antiarthritic agents in the world. Although over 60 reports of adverse ocular events possibly associated with this drug have been reported to the Registry, most are of little consequence and primarily consist of transient blurred vision. However, there is either a nonrelated chance event occurring or a rare idiosyncratic optic nerve response associated with the use of this drug. The typical clinical sequence seen in patients on ibuprofen therapy after one to three weeks is a unilateral marked decrease in visual acuity, with vision receding to 20/80 to 20/200 range. Visual fields show various types of central scotomas. If the medication is stopped, visual acuity returns to normal in one to three months. In one case, it took eight months for color vision to return to normal.[4] With a drug so commonly used, it is not possible to implicate specifically this agent. However, many of our cases are outside the usual optic or retrobulbar neuritis age group and occur shortly after starting this medication. We are interested if other ophthalmologists have seen cases similar to those reported to the Registry.

5-FLUOROURACIL

This agent is finding increasing use intravenously in the palliative management of neoplastic disease, by direct injection for the treatment of cutaneous basal and squamous cell carcinoma, and topically for the treatment of actinic keratosis.

The intravenous use of this drug is associated with irritative conjunctivitis, which includes excessive tearing, conjunctival injection, blepharitis, and some discharge.[5] A direct correlation between the amount of lacrimation and the concentration of the drug in the tears has been found.[6] The systemic use of the drug has also been associated with canalicular fibrosis[4] or increased skin pigmentation in areas exposed to the sun. Oculomotor disturbances, especially weakness of convergence or divergence probably due to regional fluorouracil neurotoxicity affecting the brain stem, have been described.[7]

In two cases reported to the Registry, direct injection of 5-fluorouracil into skin tumors on the eyelids has caused ectropion from secondary scarring, which required surgical correction. As with intravenous administration, increased skin pigmentation was also reported.

When using 5-fluorouracil topically for actinic keratosis, care must be taken to keep the drug away from the eye. Since this agent is highly irritating, it can cause significant allergic contact dermatitis.

DRUG-INDUCED OCULAR "PSEUDOPEMPHIGOID"

There is evidence that a slowly progressive drug-related cicatricial process of the conjunctiva may be indistinguishable clinically from ocular cicatricial pemphigoid. In the literature, as well as the Registry, there have been cases due to long-term use of topical ocular epinephrine[8] or echothiophate iodide[9] preparations which cause a "pseudopemphigoid" ocular pic-

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Discussion
by
Carl Kupfer, MD*

Dr. Fraunfelder has demonstrated enthusiasm and perseverance in the difficult task of establishing and maintaining a National Registry of Possible Drug-Induced Ocular Side Effects. Certainly, this activity can play an important role as an early warning system in alerting the practitioner to possible adverse effects of drugs that are being used in the diagnosis and treatment of ocular and systemic disease.

One should keep in mind, however, that the maximal utilization of a National Registry such as this is impeded somewhat by three problems. As with many other registries throughout the country, the question of under-reporting must be addressed. There is every reason to believe that ophthalmologists do not routinely report all untoward drug side effects. Questioning of the patient receiving drugs is necessary for many such side effects to be identified. Thus, the incidence of adverse effects probably represents a low estimate, but one cannot determine precisely by how much the incidence is under-reported.

A second consideration deals with determining the size of the denominator. If untoward side effects are reported in ten patients receiving drug A, which has been used perhaps on 100,000 patients, then this drug produces an adverse reaction in 1 out of every 10,000 patients treated, or a frequency of 0.01%. Perhaps the benefits do not justify the small but significant incidence of adverse effects. The knowledge of both adverse effects as well as the number of patients treated is necessary to determine the importance of this. On the other hand, if 100 cases of an adverse reaction are reported in association with drug B, but this drug is administered to perhaps 100 million patients a year, then the frequency of side effects is one in a million or 0.0001% and one would be inclined to view the benefit risk ratio in a different light. Thus, both the number of patients affected by the drug as well as the number of patients receiving the drug must be determined before a true assessment of the magnitude of the side effects can be assessed.

The third consideration is probably the most difficult one with which to come to grips, for it deals with the problem of coincidence. If one uses a drug routinely on almost every patient seen in an ophthalmologic practice, let us say for diagnostic purposes, one would expect to find from time to time that a patient may have signs and symptoms which would suggest an adverse reaction to the drug. On the other hand, examinations in the ophthalmologist's office of patients in the older age groups and whose level of anxiety may be elevated by their eye complaints may produce signs and symptoms of fainting, palpitations, dizziness, nausea, vomiting, and even coronary thrombosis and cerebrovascular accident. Whether these are coincidental to the administration of the drug in question or causally related is most difficult to determine.

Dr. Fraunfelder is fully aware of these problems and accordingly has spent his efforts and energies in alerting the profession in a more qualitative way to the possible adverse reactions one might see in an ophthalmologic practice. To this time consuming and laborious effort, Dr. Fraunfelder has brought a dedication and determination. This effort is to be commended.

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Dr. CROUT. I am surprised at that. I would not have expected them to send out information except that which was in individual case reports in their files.

Mr. GORE. You were in charge of the survey. It is your ultimate responsibility, is it not?

Dr. CROUT. The registry reports to the Bureau, and you are correct. As soon as this hearing is over I will go back and see how that survey reports out information. I would agree that report does not have a high degree of scientific credibility.

Mr. GORE. You are project officer and send them the money to do this. You are responsible for spending public money for this registry which ends up giving ophthalmologists all over the United States this questionable data.

Dr. CROUT. But we use those registries in different ways. One way is to query them. We ask them questions and they send us back information. That is why we want registries like this. The most useful way to use those registries from our standpoint is to do that.

Registries may also write papers on their own. Whether they are accurate or not depends on the investigator himself.

Mr. GORE. If you are running the registry and the project officer in charge of it and in charge of paying money sends you information for the registry, you take it; right?

Dr. CROUT. Not necessarily. It is quite obvious we have to straighten out what they take as scientific information——

Mr. GORE. You have to straighten out more than that, I am afraid.

Dr. CROUT [continuing]. And publish from that registry.

Mr. GORE. Were you aware that Mrs. Bruch intervened on behalf of Burton & Parsons concerning an inspection at its Baltimore plant?

Dr. CROUT. I know that sequence of events. I believe the phraseology "intervened on behalf of Burton & Parsons" is not the correct connotation.

Mr. GORE. How would you phrase it?

Dr. CROUT. That is standard operating procedure. This is staff working together.

In listening to the whole sequence of events and reviewing those memoranda, I think there has been the wrong connotation applied to her role. If I may for a moment describe how we are organized.

We have, in the Bureau, divisions that review new drug applications. Dr. Gibson is director of one of those divisions. Mrs. Bruch works in that division.

In another division of our Bureau there is an interaction between our compliance officers and our field inspectors.

Mr. GORE. All right.

Dr. CROUT. The decision to approve a plant for being in compliance with GMP's is made by the people in the compliance division.

Mr. GORE. Not in this case.

Dr. CROUT. Yes.

Mr. GORE. In this case the approval was granted without a final inspection. The inspector's report was overruled at the central office and it was granted without a final inspection. You are telling us that is standard operating procedure?

Dr. CROUT. That is not correct. That is not a correct sequence of events as far as I can tell from looking at the record.

Mr. GORE. Wait a minute. Let's clarify this point. You are saying that there was a final inspection before the approval?

Dr. CROUT. No. What I am saying is that there was an inspection in October at which certain problems were identified, so the plant was judged as not yet meeting GMP's.

Mr. GORE. That was after she intervened the first time, or after she contacted——

Dr. CROUT. Intervening is the incorrect word. She has to get from that division in the Bureau a determination on whether the plant is within GMP's in order to complete a review on the application in front of her, so it is quite common—indeed it is urged—that reviewers contact that compliance division and say, "Please give me your opinion on whether or not the plant is——

Mr. GORE. Did they contact her and ask her for her review of it or did she contact them on her own initiative after initiating the review herself?

Dr. CROUT. She would on her own initiative, and properly so——

Mr. GORE Go out to Burton and——

Dr. CROUT. No.

Mr. GORE. G. & S.?

Dr. CROUT. No. She would ask the compliance division for an opinion on whether or not the plant was in compliance with GMP's. That is standard operating procedure.

Mr. GORE. That is not what they say. They say she contacted them. They say, "We were visited"—and this is the manufacturing review branch, and this is an example that you are now telling us is standard operating procedure—they say "We were visited by Mrs. Mary Bruch who stated that she had been assured by representatives of this firm that all deficiencies had been corrected."

If the manufacturing review branch inspects and they find deficiencies and do not approve it, is it standard operating procedure for somebody else in another division, on their own initiative, to go contact them and say, "No problem. I have been contacted by this company. They have told me everything is all right."? Is that standard operating procedure?

Dr. CROUT. Obviously not, not in the connotation you stated it.

Mr. GORE. Put any connotation you want on it. That is what happened in this case.

Dr. CROUT. I am sorry——

Mr. GORE. Do you disagree with that much?

Dr. CROUT. Yes. I do not believe you are giving me a chance to say what I think happened.

Mr. GORE. All right.

Dr. CROUT. I could be wrong, but I am saying what, as far as I know, happened. What happened is that the plant was inspected by the Baltimore inspector. He sent back a report saying they have not yet met their GMP's.

There was a meeting in the district office which follows after that inspection, at which time they reviewed with the district office what their corrections would be for the problems.

One of those corrections involved substituting or sterile water where they had formerly used non-sterile water. That correction

was reported back to the new drug application being monitored by, being reviewed by, Mrs. Bruch.

Mrs. Bruch has every reason to——

Mr. GORE. That comes later. That is the second reinspection. I am talking about the first time that she visits. This is September 22, 1977. She goes to the manufacturing review branch, and on her own initiative states that she had been assured by representatives of this firm——

Dr. CROUT. And asked for a reinspection. Perfectly proper.

Mr. GORE. Is that standard operating procedure?

Dr. CROUT. That is standard operating procedure.

Mr. GORE. That is unusual, is it not?

Dr. CROUT. No.

Mr. GORE. Anybody in another branch can take it upon themselves to go to the manufacturing review branch and say, "Look, take it from me; I have talked to these people in the company. It is all right."?

Dr. CROUT. I don't believe that is what the request was. It is not a "take it from me, it is all right." It is that the firm has reported to me that they have made these corrections. "Would you please inspect them, verify that, and tell me your opinion"?

Mr. GORE. And then they subsequently reinspect it and find they had not been taken care of, that deficiencies of a serious nature still existed, and then on September—excuse me. They reinspect this in October.

Dr. CROUT. That is correct.

Mr. GORE. They still found the deficiencies.

Dr. CROUT. Yes, some of the deficiencies.

Mr. GORE. The approval was subsequently granted without a final, a third and final, inspection; is that right?

Dr. CROUT. It was without a third and final inspection, but there were some intervening events. There was a meeting in the district office on October 26, which I have a memorandum of if you like, at which time the firm told the district they felt they had corrected these problems, or would correct them——

Mr. GORE. Who did representatives of the firm tell that to?

Dr. CROUT. According to this they met with Cyril W. Cruchon, a compliance officer, and Miss Paula J. Oliver, supervisory investigator in the Baltimore district.

Mr. GORE. Based on assurances of the company, after they failed one inspection, then they gave assurances they would take care of it. They had a second inspection and there were still serious deficiencies. Then they gave another set of assurances. You said, "Good enough for us." Is that right?

Dr. CROUT. No.

Mr. GORE. Was there another inspection? Doctor, was there a third inspection?

Dr. CROUT. There was not a third inspection.

Mr. GORE. Is that standard procedure, to give an approval without a third inspection in circumstances like this?

Dr. CROUT. To my knowledge standard procedure was followed here, yes.

Mr. GORE. Wait a minute. I want to get the question and answer clearly. Inspected—there were deficiencies. You were assured they

would take care of them. Inspected again. They were not taken care of. Another set of assurances, and based on that second set of assurances you said, "That is good enough for us." Is that right?

Dr. CROUT. No.

Mr. GORE. What is wrong about it?

Dr. CROUT. The first time they were inspected, as I understand it, there were a number of deficiencies. A number were corrected.

By the time of the second inspection, the two serious deficiencies related to the use of nonsterile water at a certain point where sterile saline should be used.

The firm agreed to use sterile saline in that step, and that solved the problem as far as the district is concerned and as far as our compliance people were concerned.

Mr. GORE. Would that have solved the problem had it been done? However, you had no assurance other than the assurance from the company that it was going to be done. Is that correct?

Dr. CROUT. That is correct. We did not——

Mr. GORE. Is that normal procedure?

Dr. CROUT. That is a standard operating procedure.

Mr. GORE. Let me ask you to pause in your testimony for a moment. I want to call another witness to join you at the stand, Mr. Ed Thomas.

Is he here?

Dr. CROUT. May I describe what I understand the policy to be?

Mr. GORE. Not right now. I will get back to you.

Mr. Ed Thomas, if you would join Dr. Gibson and Dr. Crout at the witness stand.

Raise your right hand and be sworn.

Do you swear to tell the truth, the whole truth, and nothing but the truth, so help you God?

Mr. THOMAS. I do.

Mr. GORE. I apologize for calling you up here without advance notice.

You were the inspector on this plant. Is that correct?

TESTIMONY OF EDWARD THOMAS, COMPLIANCE OFFICER, BALTIMORE DISTRICT OFFICE, FOOD AND DRUG ADMINISTRATION, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. THOMAS. That is correct.

Mr. GORE. Let me assure you ahead of time that this subcommittee has a pretty good record for insuring protection of anybody who exercises total candor. I mean by that no implication that you would suffer retribution. I don't think you would. However, let me encourage you to be candid.

You inspected this plant on two occasions. Is that correct?

Mr. THOMAS. That is correct.

Mr. GORE. On the second inspection you found serious deficiencies still existing at the plant. Is that correct?

Mr. THOMAS. During the October inspection, yes.

Mr. GORE. Was there a third inspection prior to the approval of this plant's operation?

Mr. THOMAS. There was none conducted by the Baltimore office.

Mr. GORE. Is that standard operating procedure? Have you ever known it to happen in your career at the FDA?

Mr. THOMAS. You mean regarding the NDA inspections? I have conducted only one NDA inspection.

Mr. GORE. Do you have any basis upon which to say that that is standard or not?

Mr. THOMAS. The only other criterion I can judge by is normal regulatory inspections. With NDA inspections, it is different because the regulatory action is either approval or non-approval. The normal regulatory inspections we do, if we run into a firm which says we will do something, we indeed go back and see to it they do it.

Mr. GORE. How many of these other kinds of inspections have you conducted in your career?

Mr. THOMAS. Several hundred.

Mr. GORE. Several hundred?

Mr. THOMAS. Yes.

Mr. GORE. On any of those occasions have you seen an approval granted prior to a final inspection?

Mr. THOMAS. Again if you talk about NDA——

Mr. GORE. I am talking about the regular inspections.

Mr. THOMAS. Approval doesn't mean anything to me in that context.

Mr. GORE. Did you consider the procedure used in this instance unusual?

Mr. THOMAS. Which procedure are you talking about?

Mr. GORE. The contacting of the manufacturing review branch folks by Mrs. Bruch and the assurances given based on conversations with the company people and the subsequent approval of their NDA without a final inspection?

Mr. THOMAS. Again, I have conducted only one. The inspections and procedures which occur within the Bureau I have no knowledge of.

Mr. GORE. Would you normally sign off on a regulatory inspection without going back to assure yourself with a personal visit that the deficiencies had been taken care of?

Mr. THOMAS. During a regulatory inspection we do go back and check; yes.

Mr. GORE. In the hundreds of regulatory inspections you have conducted, have you ever seen a signoff without a return visit?

Mr. THOMAS. Again it depends on the severity of the deviations we uncover during the inspection.

Mr. GORE. In this case the deficiencies were characterized as severe. Is that right?

Mr. THOMAS. Yes. The district's recommendation was nonapproval.

Mr. GORE. The district recommended nonapproval. Then subsequently approval was granted without a final visit.

Mr. THOMAS. Baltimore did not make it.

Mr. GORE. Baltimore did not make a final visit?

Mr. THOMAS. That is correct.

Mr. GORE. Thank you very much.

Dr. Crout, I will give you a chance to continue your response. We will recess for about 8 minutes and then resume. I anticipate wrapping this hearing up within 20 minutes.

We will be back in 8 minutes.

[Brief recess.]

Mr. GORE. The subcommittee will be in order.

Let me ask you, Dr. Crout, whether you think it is a good policy to go ahead and approve an NDA after two inspections have shown serious deficiencies without a final inspection prior to approval.

TESTIMONY OF DR. J. RICHARD CROUT AND DR. MERLE L. GIBSON—Resumed

Dr. CROUT. Yes, there is nothing wrong with that policy, if I may describe the circumstances. The policy is that GMP violations can be corrected by the firm, must be corrected by the firm. However, evidence of that correction may come in in a new drug application, as it did in this case, or it may require reinspection. The decision on whether to have a reinspection is made by our compliance people, and in this case they felt no reinspection was necessary.

The sole point at issue was whether or not the firm was going to use sterile saline instead of unsterile water for the rehydration of those lenses. That is a problem——

Mr. GORE. There were eight deficiencies.

Dr. CROUT. The key ones, by the time of the second inspection, were ones known as deficiencies 7 and 11.

Mr. GORE. There were eight deficiencies on the second inspection.

Dr. CROUT. But the ones of importance were judged to be only 7 and 11 by our compliance people.

Mr. GORE. After approval they still found some deficiencies.

Dr. CROUT. Not ones sufficient to prevent approval. That is their job.

Mr. GORE. The approval already occurred.

Dr. CROUT. I am not aware of what you are referring to now.

Mr. GORE. Approval was on December 12. There was no reinspection after the date in October. In a memo to the manufacturing review branch from the Baltimore district they say——

Dr. CROUT. Dated when, sir, so I can follow the file?

Mr. GORE. Dated December 12, 1977. They say, "In regard to this firm's compliance with CGMP we believe improvement has been made and there is room for additional improvement. However, we believe the deviations noted during this inspection do not warrant further regulatory action."

Therefore, it is true that after the final approval, they went back after the final approval, they still found some deviations but decided not to reopen it.

Dr. CROUT. This memorandum of December 12, 1977, represents the final opinion of the manufacturing review branch. The application itself was not approved until April 27, 1978, some 4 months later.

Mr. GORE. We had a little hassle with your office concerning Dr. Seife who was reprimanded for frequent lunches with the industry. Do you remember the cost of the most expensive lunch involved in that case?

Dr. CROUT. That is not a matter I looked into.

Mr. GORE. Is it fair to say the lunches were of nominal value?

Dr. CROUT. Yes.

Mr. GORE. Is it fair to say none of the lunches approached $149.50?

Dr. CROUT. Not to my knowledge.

Mr. GORE. A recent case involved your Bureau, the case that I just mentioned, Dr. Seife and others, where individuals were detailed out of the division pending completion of the investigation. Do you think that is a good procedure?

Dr. CROUT. I think in that circumstance it was. This occurred late in the investigation, and at that time there were five people who, to some extent, had allegations going back and forth among each other.

Mr. GORE. You are not sure whether that is appropriate in this case?

Dr. CROUT. And in addition the work of the division was really suffering.

In this circumstance now, it is early in the investigation from our standpoint—it may well be late from your standpoint, but from ours it is early. Second, the two employees, Mrs. Bruch and Dr. Scafidi, are not handling soft lenses anymore. They are handled by the Bureau of Medical Devices.

Mr. GORE. You mentioned in your statement an investigation by your policy management staff of the FDA concerning issues raised by the subcommittee. I would like, one, to inform you that there is an investigation currently underway by the Inspector General; two, in view of the potential criminal charges that could be brought in connection with this investigation, it seems appropriate for the IG's office to continue its investigation to the exclusion of the FDA's own internal staff. It appears clear to me that the Bureau of Drugs personnel are not in a position to undertake an objective investigation of this issue.

I would like——

Dr. CROUT. Excuse me; the policy management staff is in the Commissioner's office. I am certain they will work out an arrangement with the IG.

Mr. GORE. Dr. Gibson, the June 1976 action memo to you from Dr. Finkel [see p. 67] called for an arrangement with the salt tablets. Why did you not carry out that decision?

Dr. GIBSON. The original memorandum which went forth to Dr. Finkel recommended several things, including removing salt tablets. Her response to me indicated consideration——

Mr. GORE. It did not recommend removal of salt tablets.

Dr. GIBSON. You mean——

Mr. GORE. June of 1976 recommended a labeling change.

Dr. GIBSON. That is her response to me. The original memorandum to which this memorandum is a response had two issues in it—one was the salt tablet issue and the other was labeling lens care solutions with the lenses that were approved and tested against them.

Her idea was to consider a Federal Register statement. This never came about. The Federal Register statement was not done. It was about that time in 1976 that Mr. Dodd of Bausch & Lomb had indicated that the intent of Bausch & Lomb was to phase out the

salt tablets when they had a preserved saline which was satisfactory.

Mr. GORE. I have a number of other questions for each of you. However, we have a series of four votes on the floor which will delay a reconvening of this subcommittee for quite some time.

In light of that fact, I am wondering whether the two of you would be willing to respond to these additional questions.

Would that be agreeable?

Dr. CROUT. I am trying to go on vacation for the next 3 weeks.

Mr. GORE. That would be fine with us.

Dr. CROUT. Thank you.

Mr. GORE. If we can get them pretty soon after that.

I would like to close the hearing by putting into the record at this point a list of steps which should be taken to insure the proper use of salt tablets.

[The information referred to follows:]

(From Consumer Reports, June 1980)

The controversy over salt tablets

Disinfection is one of the daily nuisances and expenses of wearing soft lenses. With heat disinfection, much of that cost is for the saline solution used in rinsing, disinfecting, and soaking the lenses. Until a few years ago, a million or more soft-lens wearers were mixing one Bausch & Lomb salt tablet with one ounce of distilled water to prepare a batch of saline solution to use each day. Cost: about $10 a year for tablets and water.

In a July 1977 letter to practitioners, Bausch & Lomb touted salt tablets as "safe, effective, economical, and convenient." But, in November 1978, the company decided to stop marketing salt tablets. Consumers were forced to buy bottles of premixed, preserved saline sold by Bausch & Lomb and other companies. Cost: about $40 a year, or 300 percent more than the cost of tablet-made saline. What's more, the preservative in the premixed solutions (thimerosal) causes eye irritation in about 20 percent of users. Preservative-free saline is also available, but it can cost as much as $140 a year.

The removal of salt tablets from the market outraged many consumers. They wrote angry letters to Bausch & Lomb (and to CU) charging that the company stopped marketing the tablets because its preserved saline was more profitable. But it wasn't as simple as that. Bausch & Lomb's switch was triggered, in part at least, by the Government's concern over the use of salt tablets.

FDA officials contended that soft-lens wearers were misusing the tablets in several ways: They used the wrong kind of water; the saline they made up was often too salty or not salty enough for the eyes; and most important, their distilled water was often contaminated with bacteria, which could infect the eye. Since salt tablets contained no preservatives, bacteria could multiply in contaminated water used to make saline. A contact lens soaked in this saline could transmit bacteria to the cornea, and an abrasion could then allow bacteria to penetrate the cornea and cause a serious infection.

FDA officials acknowledged that daily use of a heating unit would kill all types of bacteria and eliminate any risk from contaminated saline. But they contended that many people didn't use their heating units every day. To support their argument, officials could point to about 20 cases in which corneal infections among salt-tablet users could be traced to contaminated saline. (Severe infections, however, had also occurred with preserved saline.)

It was this line of reasoning that led to a letter, dated May 15, 1978, from David Link, director of the FDA's Bureau of Medical Devices, to Bausch & Lomb. He wrote: "FDA would appreciate communication from you to develop a schedule with you for the immediate withdrawal of the salt tablets from the marketplace." Six months later, Bausch & Lomb removed salt tablets from the market, although Link now says the FDA "did not order the removal of salt tablets."

An FDA advisory panel, however, has not been convinced that salt tablets are dangerous. Earlier this year it recommended that salt tablets be allowed on the market, provided that future studies show they are safe to use.

CU's consultants also believe that salt tablets can be used safely. What's more, they point out, the tablets are noninvitating and are the least expensive source of saline. Along with many other practitioners, our consultants are advising patients that they can use other salt tablets now on the market, provided they take the following precautions:

1. Use only distilled water or purified water labeled U.S.P. (United States Pharmacopeia). Tap water, and even "demineralized" or "deionized" water, may contain minerals such as iron or calcium that can cause problems. Keep the water refrigerated to reduce bacterial growth.

2. Use only U.S.P. salt tablets. Others, such as those used for heat sanitation, may contain added chemicals. Companies selling U.S.P. tablets include Blairex Laboratories Inc., Martin Industries, and Eli Lilly Co. Mix one ounce of distilled water with each 250-milligram salt tablet (or four ounces of water with the 1000-milligram Eli Lilly tablet).

3. Make a fresh batch of saline solution each day. Never re-use solution. And never use leftover saline solution to moisten the eyes or the lens.

4. Keep the vial in which the solution is prepared scrupulously clean. Rinse it daily with hot tap water.

5. Use the heating unit each time you take your lenses out. (It's the heating unit, not the saline, that disinfects.)

6. If lenses have not been worn for a week or more, add fresh saline and disinfect again before wearing them.

(NOTE: The Food and Drug Administration (FDA) has granted approval for Marketing of salt tablets. The instructions for use recommended by FDA should be followed.)

Mr. GORE. The hearing record today calls for further action. Prior to this hearing, I discussed this matter with Chairman Eckhardt. We agreed that if facts were established as they appeared to be before the hearing, then the entire matter should be referred to the Inspector General's Office and to FDA Commissioner Goyan for further attention. I think such a record has been established.

It is especially appropriate in this instance to refer the case in this manner. The Inspector General's office has a pending investigation and the matter is referred to that office for appropriate attention under its statutory authority set forth in Public Law 94-505. Further, the Commissioner has recently had to deal with other questions relating to management and standards of conduct within the Bureau of Drugs. I would ask the Commissioner to report to the subcommittee within 30 days and advise what steps he has taken, or is contemplating taking, to insure the subcommittee that the regulatory abuses chronicled today will not be repeated.

The subcommittee stands adjourned.

[Whereupon, at 2:10 p.m., the subcommitted adjourned.]

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